

August 2013

NIEHS Spotlight



[East meets west at international toxicology congress in Seoul](#)

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[NIEHS sets the standard for protocol transfers](#)

Three Institutional Review Board protocols have been transferred from the National Institute on Aging to NIEHS oversight and three more are in progress.



[Mitch Eddy honored for distinguished service at SSR annual meeting](#)

NIEHS lead researcher Edward Mitchell (Mitch) Eddy, Ph.D., received the Society for the Study of Reproduction award July 23 at the group's annual meeting in Montreal.



[Concept paper emphasizes environmental influences on individual organisms](#)

Superfund Research Program grantee Dietmar Kùltz, Ph.D., is the first author of a new concept paper that calls for a renewed emphasis on organismal, or integrated biology.

Science Notebook



[Bringing down the Tower of Babel in data sharing](#)

The difficulty of developing a consistent nomenclature for searches of multiple databases was the focus of a workshop sponsored by NIEHS and EPA June 25.



[Talking toxicogenomics and global database](#)

More than 30 scientists from around the world involved with toxicogenomics databases attended an international meeting at NIEHS June 26-27 on how to coordinate resources.



[Exciting developments in Huntington's disease research](#)

The Keystone Science Lecture Seminar Series continued June 27 with a lecture by Cynthia McMurray, Ph.D., on new findings about neurodegenerative disease.



[A plan for revolutionizing toxicology testing for the 21st century](#)

A predictive toxicology toolkit seeks to revolutionize the field, opening up avenues for biomarker identification, identification of nonhazardous chemicals, and green design.

NIEHS Spotlight



[Critical gaps in household air pollution research identified](#)

Household air pollution from smoky inefficient cookstoves affects nearly 3 billion people, almost half the world's population.



[Workshop addresses contaminants of emerging concern in drinking water](#)

Experts gathered at a workshop July 10-11 in Washington, D.C., to discuss issues associated with contaminants of emerging concern in drinking water.



[ONES awardee honored by Burroughs Wellcome](#)

Vishal Vaidya, Ph.D., is one of five North American scientists selected to receive 2013 Burroughs Wellcome Innovation in Regulatory Science Awards.



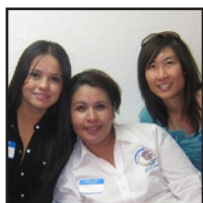
[Grantee Gary Miller named ToxSci editor-in-chief](#)

The Society of Toxicology Board of Publications announced July 23 the selection of NIEHS grantee Gary Miller, Ph.D., as editor in chief of Toxicological Sciences.



[Martin named dean of Ohio State University College of Public Health](#)

Former NIEHS associate director Bill Martin, M.D., leaves a post at NIH in August to lead the College of Public Health at Ohio State University.



[Superfund pilots new promotora training module in Mexico and Arizona](#)

The University of Arizona Superfund piloted the latest promotora training module this summer on everyday health risks from environmental exposures.

Science Notebook



[LSB speaker discusses the role of RNase H2 in Aicardi-Goutieres Syndrome](#)

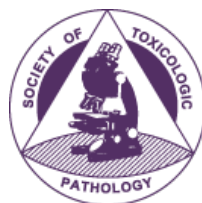
A June 21 seminar at NIEHS focused on two interesting consequences of unremoved ribonucleotides misincorporated into DNA — genomic instability and growth arrest.



National Institutes of Health

[NIEHS fellows honored with 2014 FARE awards](#)

NIEHS continued its tradition of research excellence as 19 of its fellows received the 2014 Fellows Award for Research Excellence this summer.



[NTP postdocs recognized with Society for Toxicologic Pathology awards](#)

NTP postdocs won two of the three Young Investigator Awards presented at this year's Society of Toxicologic Pathology annual meeting June 16-20 in Portland.



[NIEHS and NTP join colleagues at Teratology Society meeting](#)

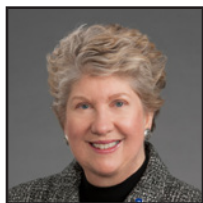
NIEHS and NTP scientists gave a number of cutting-edge talks at the society's 53rd annual meeting June 22-26 in Tucson, Ariz.



[Indian scholar offers global perspective on fiber nanotoxicology](#)

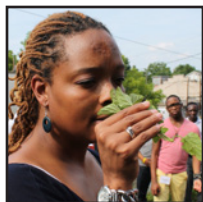
Qamar Rahman, Ph.D., dean of Research Science and Technology at Amity University in India, visited NIEHS July 19 to deliver an eye-opening talk on nanotoxicology.

NIEHS Spotlight



[Migrant farmworker housing fails to provide relief from heat](#)

Researchers led by Sara Quandt, Ph.D., of Wake Forest School of Medicine, report new findings with implications for worker safety and health.



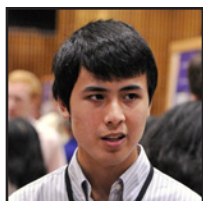
[Duke workshop addresses environmental justice issues in North Carolina](#)

Environmental justice, exposure to toxic chemicals, and sustainability were the topics of a workshop hosted by the NIEHS-funded Duke University Superfund Program.



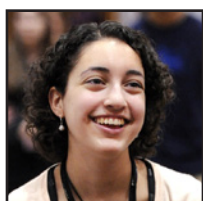
[LMG fellow begins independent career in Israel](#)

Former NIEHS Laboratory of Molecular Genetics postdoc Shay Covo, Ph.D., began a new career in June as an assistant professor at The Hebrew University of Jerusalem.



[Research is generational for Falk grandson](#)

NIEHS summer intern Michael Falk is forging his own research path by working out a bioinformatics strategy as part of the Mouse Methylome Project.



[Intern-led research takes center stage at 2013 summer poster session](#)

Following three months of seminars, workshops, career panels, and research training, the 2013 NIH Summer Internship Program at NIEHS drew to a close July 25.

Science Notebook



[NIEHS scientists find proteins involved in immunity potentially cause cancer](#)

A set of proteins involved in the body's natural defenses produces a large number of mutations in human DNA, according to a new study led by researchers at NIEHS.



[Watching a polymerase be unfaithful in real time](#)

A new X-ray crystallography technique confirmed features of the computational results an NIEHS-led team generated earlier, but revealed important surprises.



[Using gene expression data to map the mouse brain](#)

In a study published online July 14 in *Nature Neuroscience*, NIEHS neurobiologists revealed, for the first time, a roadmap of norepinephrine neurons in the rodent brain.



[Promising environmental health researchers receive Superfund award](#)

Five exceptional Superfund trainees received the 2013 K.C. Donnelly Externship Award Supplement to enrich their research in environmental health science.



[PEPH webinar focuses on the health of our oceans](#)

PEPH hosted a webinar July 10 highlighting some of the cutting-edge marine research underway at two of the NIEHS/NSF Centers for Oceans and Human Health.

Inside the Institute



[NIEHS volunteers support science day camp](#)

The Durham Alumnae Chapter of Delta Sigma Theta Sorority attracted more than 40 students to its 8th annual summer science day camp June 22.



[It's summertime and the visitors flock to NIEHS](#)

NIEHS welcomes visitors all year, but when June arrives the number of guests increases dramatically as summer program students participate in tours of the Institute.

Science Notebook



[This month in EHP](#)

This month, Environmental Health Perspectives highlights efforts to reduce pollution caused by artisanal brick kilns and implications of a Supreme Court ruling for genetic research.

Extramural Research

[Extramural papers of the month](#)

- [Mouse study points to possible gene-environment interaction for schizophrenia](#)
- [Improving health for low-income workers](#)
- [Metabolomics reveals early changes in metabolic pathways for Alzheimer's disease](#)
- [Brd4 insulates chromatin from DNA damage signaling](#)

Intramural Research

[Intramural papers of the month](#)

- [Ultraviolet radiation exposure associated with autoimmune diseases in juveniles](#)
- [Acrolein-induced adducts may cause mutations in mitochondria](#)
- [Interaction of Prox1 with RORs modulates circadian clock and metabolic regulatory networks in liver](#)
- [Mutations cause antagonist reversal activity of estrogen receptor alpha](#)

Calendar of Upcoming Events

- **Aug. 5**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Laboratory of Molecular Genetics Fellows Invited Speaker Series presentation on “DNA glycosylases search for and destroy oxidized DNA bases,” by Susan Wallace, Ph.D.
- **Aug. 6**, in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group with Heather Patisaul, Ph.D., discussing “Endocrine Disruption of Neuroendocrine Pathways”
- **Aug. 8**, in Rodbell A, 11:00 a.m.-12:00 p.m. — Laboratory of Reproductive and Developmental Toxicology Seminar Series presentation on “Towards the Establishment of Rapid In Vitro Assay Systems for Chemical Toxicity Using Mouse Artificial Chromosomes,” by Mitsuo Oshimura, Ph.D.
- **Aug. 9 (offsite event)**, at RTI International Dreyfus Auditorium in Research Triangle Park, N.C., 8:15 a.m.-5:00 p.m. — NIH Eastern Regional Comprehensive Metabolomics Resource Core Symposium, [register](#)
- **Aug. 9**, webinar, 2:00-3:30 p.m. — Partnerships for Environmental Public Health “Reaching Our STEM Potential — How Can We Improve Our Performance in Science, Technology, Engineering, and Math?” register at http://bit.ly/PEPH_STEM
- **Aug. 12**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Laboratory of Molecular Genetics Fellows Invited Speaker Series presentation by Yves Pommier, M.D., Ph.D., topic TBA
- **Aug. 14**, webinar, 1:00-2:30 p.m. — EPA/NIEHS Children’s Centers 2013 Webinar Series, featuring Issac Pessah, Ph.D., and Rebecca Schmidt, Ph.D., <http://www.epa.gov/ncer/childrenscenters/webinar/2013/overview.html>
- **Aug. 19**, in Keystone 2164, 10:00-11:00 a.m. — NTP Toxicology Branch Seminar on “Zebrafish as a tool for Screening and Prioritization of Chemicals for Toxicity Testing,” by Arantza Muriana, Ph.D.
- View More Events: [NIEHS Public Calendar](#)

East meets west at international toxicology congress in Seoul

By Eddy Ball

As one of global toxicology's leading figures, NIEHS and NTP Director Linda Birnbaum, Ph.D., presented a keynote lecture July 2, and chaired sessions, at an international meeting devoted to translational toxicology.

Birnbaum led the six-member U.S. National Toxicology Program (NTP) delegation to the [XIII International Congress of Toxicology 2013 \(ICT2013\)](#) June 30-July 4 in Seoul, South Korea, where they joined a number of NIEHS grantees who also made presentations. The U.S. NTP delegation participated in sessions on the development of high throughput screening-based predictive toxicology, by sharing advances in the U.S. interagency Toxicology in the 21st Century (Tox21) program.

During the meeting, representatives of the U.S. NTP and Korean NTP also discussed international partnerships and participated in a meeting of the International Cooperation on Alternative Test Methods (ICATM). NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Acting Director Warren Casey, Ph.D., represented the U.S. in discussions with colleagues from around the world ([see text box](#)).

Following their formal meeting in Seoul, Birnbaum and the USNTP delegation joined representatives of the Korean NTP July 5 for a one-day post-congress retreat to continue their discussions.

In a pre-congress meeting June 30, Birnbaum took advantage of an opportunity to meet individually with Her Royal Highness Princess Chulabhorn Mahidol of Thailand, a leading figure in promoting global public health research in Southeast Asia. NIEHS has a long history of partnerships and collaborations in the region, through its Superfund Research Program, and supports research projects there, including ones on e-waste recycling in China and Vietnam.



Following a full day of pre-congress courses and presentations, ICT2013 President Byung-Mu Lee, Dr.P.H., formally opened the congress by welcoming participants to ICT2013. (Photo courtesy of ICT2013)



Birnbaum developed a simple theme in her talk, but one whose implications challenge the foundations of contemporary biomedical research — “You Can’t Change Your Genes, but You Can Change Your Environment.” (Photo courtesy of ICT 2013)

Delivering a strong environmental public health message

Addressing an audience of toxicologists and health scientists from around the world, Birnbaum reminded her listeners of the important role environment plays in human health.

“Global environmental health matters, because noncommunicable diseases are major causes of death worldwide and underlie almost two-thirds of all global deaths,” she said. “Although all countries face epidemics of these diseases, low-income and middle-income countries, and the poorest and most vulnerable populations within them, are affected the most.”

Referring to the Global Burden of Disease Study 2010 published in [The Lancet](#) in 2012, Birnbaum delivered a litany of figures on global public health that underscored what she called a global imperative to create and implement effective prevention strategies. “At least 13 million deaths could be prevented, per year, by improving our environment,” she said.

In her review of environmental health research by NIEHS and NTP, Birnbaum discussed several emerging concepts. Among them were the developmental origins of adult disease, endocrine disruption, epigenetic modification of gene expression, mixtures, and nonmonotonic dose response to hormones and hormone-like chemicals.

The final part of Birnbaum’s presentation moved into a discussion of Tox21 and NIEHS initiatives in the area of global health. Listing the accomplishments of Tox21 during its first four years, she described the 1000 Genomes Project, a genetically diverse platform for high-throughput screening, for prioritizing suspect chemicals for advanced evaluation, and the Diversity Outbred (DO) mouse, a new population-based mouse model for identifying, characterizing, and quantifying hazard, by final-stage *in vivo* assessments of high-priority chemicals selected through high-throughput *in vitro* screening.

Birnbaum concluded with examples of the role of NIEHS as a citizen of the world, by pointing to the new strategic plan and ongoing global health initiatives. These included the Institute’s leadership in the Global Alliance for Clean Cookstoves initiative;



NTP Associate Director John Bucher, Ph.D., second from left, and Birnbaum, to his right, co-chaired the session on “National Coordination of Toxicology Research and Testing” July 2. Lead NTP scientists Mary Wolfe, Ph.D., left, and Nigel Walker, Ph.D., right, also presented the U.S. perspective, while their Korean colleagues discussed their own initiatives in toxicology. (Photo courtesy of Nigel Walker)



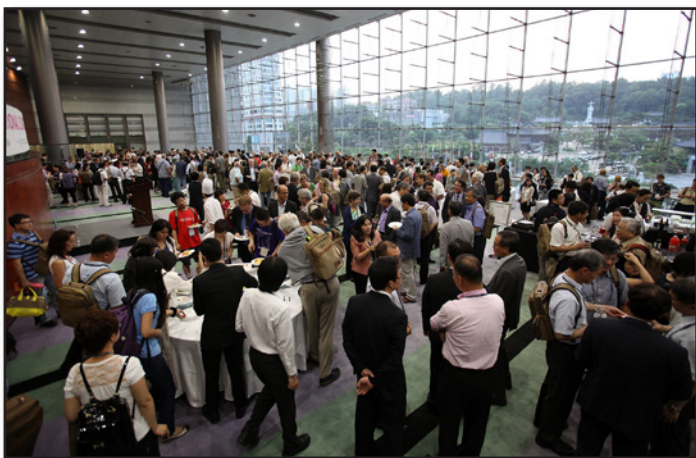
Birnbaum, right, took the opportunity to meet with Princess Chulabhorn and discuss opportunities for further collaboration in Southeast Asia. (Photo courtesy of Jutamaad Satayavivad and the Chulabhorn Research Institute)



One of the largest facilities of its kind in South Korea, the four-story COEX Convention and Exhibition Center in Seoul has four exhibition halls and 48 meeting rooms, with ample space for the ICT2013 poster sessions. (Photo courtesy of ICT2013)

collaborations in research on arsenic in drinking water, such as ongoing work in Asia and the Americas; impacts of electronic waste exposure in China, Vietnam, and other developing countries; and the health impact of climate change.

Over the following three days, Birnbaum and the NTP delegation joined experts from the U.S., Asia, and Europe in the exploration of the most effective ways to achieve the congress mission of building a translational toxicology program that progresses from basic science, to clinical and environmental outcomes, to enhance global public health.



During breaks, attendees could enjoy the mix of old and new Korea outside, as they discussed the presentations and continuing education courses offered at the meeting. (Photo courtesy of ICT2013)



In between sessions or after hours, attendees could experience a bit of Korean cultural history near the convention center, against a backdrop of the skyscrapers of modern Seoul. (Photo courtesy of ICT2013)



The U.S. NTP delegation joined their Korean counterparts, during the historic meeting. Shown, center to right, are Birnbaum, in beige, Wolfe, Walker, and Bucher. Not shown: Casey and NTP scientist Jef French, Ph.D., who spoke about development and applications of the DO mouse model. (Photo courtesy of ICT2013)

Promoting alternative testing on an international level

By Cathy Sprankle

Casey presented an update on NICEATM activities July 3 at a coordination meeting of ICATM, an international partnership that promotes the advancement of replacement, reduction, and refinement alternatives for animal testing. Casey co-chaired the session with Soon Young Han, Ph.D., director of the Toxicological Evaluation and Research Department at the National Institute of Food and Drug Safety Evaluation, part of the Korea Food and Drug Administration, who represented the Korean Centre for the Validation of Alternative Methods.

The ICATM coordination meeting in Seoul included updates from Europe, Japan, Korea, and the U.S. on their current test method evaluation and validation activities. Casey's update was titled "A New Strategic Direction for ICCVAM and NICEATM: Future Plans for the Validation and Acceptance of Alternative Test Methods in the United States." He discussed NICEATM activities supporting Tox21 and NICEATM collaborations to develop new models to identify skin sensitizers, substances with the potential to cause allergic contact dermatitis.

Finding replacements for animal testing, to identify potential skin sensitizers, was the major focus at the July ICATM meeting. However, member organization representatives also provided updates on studies of alternative test methods to identify potential eye irritants, carcinogens, and endocrine-active substances.

ICATM currently includes organizations from the European Union, U.S., Japan, Canada, and South Korea. The government of Brazil recently established the Brazilian Centre for the Validation of Alternative Methods (BraCVAM). The new center will begin participating in ICATM coordination meetings as an observer this fall.

ICATM coordination meetings take place several times a year and provide an opportunity for the five member organizations to discuss activities in the three critical areas of cooperation — validation studies, independent peer review of the validation of test methods, and the development of formal test method recommendations on alternative testing methods.. The meetings are planned to coincide with meetings of the Society of Toxicology and other gatherings of mutual interest to the participant organizations. Regular interactions allow ICATM partners to develop good communications and working relationships, which support collaborations on test method development.

(Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

[Return to Table of Contents](#)

NIEHS sets the standard for protocol transfers

By Ernie Hood

The NIEHS Human Research Protection Program (HRPP), which encompasses the NIEHS [Office of Human Research Compliance \(OHRC\)](#) and Institutional Review Board (IRB), is currently in the process of working with the National Institute on Aging (NIA), to transfer six of its clinical research protocols to NIEHS for IRB oversight.

A protocol is a predefined, written procedural method in the design and implementation of a research study. A well-written protocol is essential for answering specific research questions, avoiding problems during the study, achieving a high quality research study, and safeguarding the health of participants.

Under the leadership of Joan Pakenham, Ph.D., OHRC director and vice-chair of the IRB, NIEHS is setting the standard for future efforts of this kind. With three of the protocols already transferred and three more in progress, this marks the first time such a transfer has been successfully undertaken. One of the studies, the [Baltimore Longitudinal Study of Aging \(BLSA\)](#), is America's longest-running scientific study of human aging, having started in 1958.

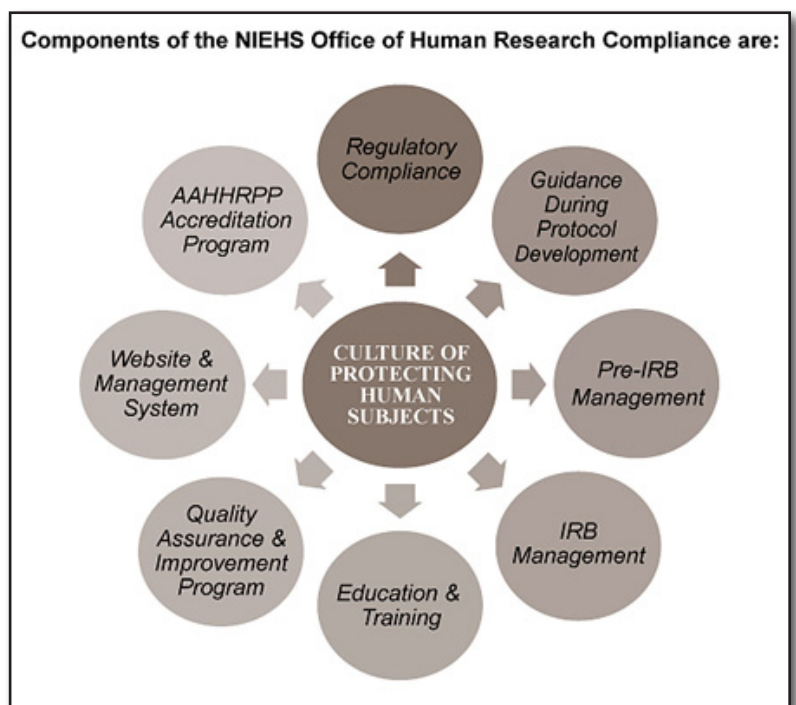
The transfer process is occurring because the NIH [HRPP](#), which includes all NIH institutes and centers (ICs), is undergoing accreditation by the [Association for the Accreditation of Human Research Protection Programs \(AAHRPP\)](#). Successful completion of the rigorous accreditation process signifies an organization's commitment to the highest standards of ethics, research quality, and protection of human subjects.

NIEHS and NTP Director Linda Birnbaum, Ph.D., said of the transfer, "Once again, NIEHS is ahead of the curve, with groundbreaking work being performed by our OHRC and being used as a model by other NIH ICs. That's pretty significant, particularly as we are going into AAHRPP accreditation."

With the accreditation process approaching, the NIH Human Subjects Research Advisory Committee (HSRAC) advised NIH Deputy Director for Intramural Research Michael Gottesman, M.D., that any ICs using commercial or external IRBs needed to transfer



"What we have done is a model for the ICs to follow and for NIH to develop policies concerning transfer of protocols," said Pakenham. (Photo courtesy of Joan Pakenham)



Among its several activities, the OHRC manages the NIEHS IRB and oversees interactions with the AAHRPP accreditation program.

their protocols in-house to NIH IRBs. Since NIA had been using a commercial IRB, it was necessary for them to transfer their protocols to one of the NIH in-house IRBs. NIEHS received six of the existing NIA protocols.

New ground, new policies

“It was an honor for NIEHS to be selected for the protocols,” Packenham said. “Most of them are epidemiological protocols with minimal risk, so you could say we’re serving as an epidemiological thematic IRB. For this type of transfer, we developed standard operating procedures, as well as a transfer agreement, that specifically indicated the necessary criteria for the transfer between NIA and us.”

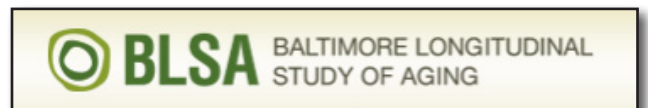
The protocol transfer process is not simple, and this type of transfer is new territory for NIH. Recognizing those challenges, the HSRAC formed a Protocol Transfer Subcommittee (PTS), and, due to the success of the NIA-NIEHS protocol transfer, Packenham was asked to be the subcommittee chair. She has overseen the protocol transfers and formulated many of the new policies and procedures necessary to complete the process.

At the HSRAC meeting June 21 at the NIH Clinical Center in Bethesda, Md., Packenham reported on the subcommittee progress, experiences, and lessons learned. Bethesda, Md.

“There are many different ways that transfers of protocols can occur, and we certainly have to have policies in place to make sure they are done properly, so that regulations and guidance are followed, everyone has the same understanding, and all are in agreement with the process, to insure that research is not affected and participants are not harmed by the transfer,” Packenham noted.

Packenham said that the current round of NIA-NIEHS protocol transfers should be completed by the end of the summer, and that the NIEHS IRB expects, in the future, to receive subsequent initial NIA protocols for new studies being started.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



BLSA, the nation’s longest-running scientific study of aging, began in 1958, when gerontology was still very much in its infancy. With more than 1,300 volunteers who made a lifelong commitment to be part of the research, BLSA continues to be an innovative and robust study. (Images courtesy of National Institute on Aging)

[Return to Table of Contents](#)

Mitch Eddy honored for distinguished service at SSR annual meeting

By Eddy Ball

NIEHS lead researcher [Edward Mitchell \(Mitch\) Eddy, Ph.D.](#), received the Society for the Study of Reproduction (SSR) Distinguished Service Award July 23 at the group's annual [meeting](#) in Montreal. "His steady contributions of leadership, mentorship, and scientific expertise have helped mold and solidify the society as we know it today," [SSR](#) said in its announcement of the award.

SSR cited Eddy's contributions over more than a decade as director, president, program chair, publications chair, and associate editor of the SSR journal [Biology of Reproduction \(BOR\)](#).

"I am delighted to learn of Mitch's richly deserved Distinguished Service Award," said NIEHS and NTP Director Linda Birnbaum, Ph.D. "Here at the Institute, as well as in the larger scientific community, Mitch makes important contributions to science and the next generation of biomedical researchers, by working quietly behind the scenes. He's a modest man, so it takes awards, such as this one, for the rest of us to fully realize just how much Mitch is giving of himself."

Moving the society and its journal into the new millennium

Since 2001, Eddy's many contributions have been instrumental in the evolution of SSR and BOR to meet the challenges of a rapidly changing scientific and publishing environment. They range from helping create the SSR strategic plan and re-vision the Publications Committee Research Ethics and Animal Ethics subcommittees, to building the foundation for the transition of BOR from print to an exclusively electronic publication.

From the beginning, Eddy played an important part in planning the scientific programs for SSR annual meetings, and his leadership quickly extended to most aspects of the society's affairs. In his most recent role as publications chair, Eddy was instrumental in initiating BOR's optimization for mobile devices, creating a BOR and SSR marketing campaign, developing the SSR website redesign project, adopting continuous publication of BOR, and revising and reorganizing the journal's instructions for authors on the Web.

The most recent milestone in a stellar career

After completion of his Ph.D. in anatomy from the University of Texas Medical Branch in 1967, Eddy went on to become an NIH postdoctoral fellow and an instructor at Harvard Medical School. He later became a member of the faculty of University



Eddy, left, received his 2012 Mentor of the Year award from Tracy Clement, Ph.D., a postdoctoral fellow in his group and LRDT representative on the NTA steering committee. (Photo courtesy of Steve McCaw)



Among Eddy's contributions to the SSR journal was development of an easily navigable, reader-friendly [information for authors and reviewers](#) page. (Image courtesy of SSR)

of Washington School of Medicine, advancing to professor in 1982, before joining NIEHS in 1983 to lead the Gamete Biology Group in the Laboratory of Reproductive and Developmental Toxicology (LRDT).

In addition to his SSR Distinguished Service Award, Eddy has received several honors, including the Distinguished Andrologist Award from the American Society of Andrology. Characteristically, one of the awards he found the most gratifying was his selection by the NIEHS Trainee's Assembly (NTA) as 2012 NIEHS Mentor of the Year.

[Return to Table of Contents](#)

Concept paper emphasizes environmental influences on individual organisms

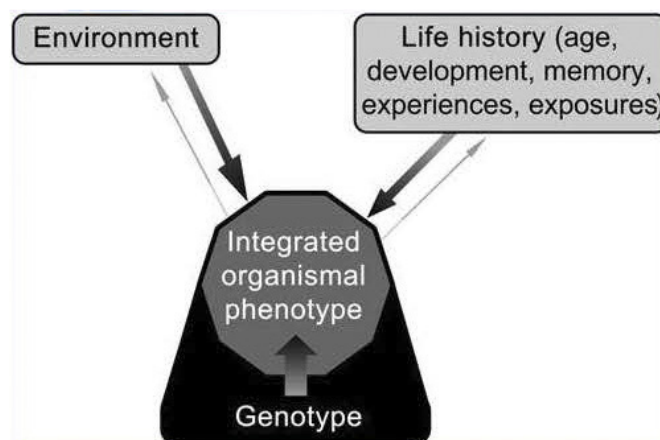
By Nancy Lamontagne

University of California, Davis (UCD) Superfund Research Program (SRP) grantee [Dietmar Kültz, Ph.D.](#), is first author of a new concept [paper](#) calling for renewed emphasis on organismal biology — the study of structure, function, ecology, and evolution at the level of the organism. Kültz and colleagues argue that their approach will help scientists better understand how environmental exposures, experienced at various life stages, produce specific biological outcomes, or phenotypes.

As the authors describe their holistic approach, organismal biology reveals general organizing principles of physiological systems and behavior, particularly in complex multicellular animals. The authors contend that biology has shifted too much toward studying genes, rather than organisms, and that genetic variation alone cannot explain the physiological and behavioral variations of complex organisms.

“Phenotyping tools and approaches for studying environmental influences on individual organisms are not nearly as mature, powerful, or trendy as approaches targeting genetic blueprints,” Kültz said. “However, a greater emphasis on in-depth, high-resolution phenotyping is critical for understanding the individual nature of an organism’s complex physiologies and behaviors.”

Kültz’s paper appeared in the journal *Bioscience*, a publication of the [American Institute of Biological Sciences](#) that highlights synthetic overviews of current biological research. The paper presents the results of analyses and discussions from a 2011 workshop on the future of organismal biology, which was supported by the National Science Foundation.



According to the authors, the three principal actors defining organismal phenotypes are the genotype of the individual, the environment in which the individual is embedded, and the life history experienced by the individual. The life history represents the sequence of environmental exposures during the course of the individual’s life — in particular, during early development — which are recorded as cellular and higher forms of memory. Organisms vary in their propensity for recording life history. (Image and caption courtesy of Dietmar Kültz)

Understanding how memories influence the organism

Kültz explained that complex physiologies and behaviors vary greatly among individual organisms, because of the many theoretical combinations in which an individual genome, the full set of genetic material, can be expressed. The way a genome is expressed is greatly influenced by learning, training, development, and other life experiences that depend on the environment an organism is exposed to at particular times.

“Thus, personalized medicine may be informed by an individual’s genetic blueprint,” Kültz said. “But life history experiences, or memories, which are recorded in the form of specific molecular, cellular, and higher-order phenotypes, must also be considered.”

According to the authors, it is important to understand how the unique sequence of environmental exposures experienced by an individual organism over its lifespan is memorized, and how the organism retrieves these memories to inform responses to subsequent environmental challenges and scenarios. This knowledge will help explain complex physiologies and behaviors, such as disease susceptibility, immunity, stress resilience, coping ability, and aging that are central to human health.

Kültz and the other authors point to needs for improved tracking technologies to monitor organisms and their natural environment, more powerful and widely accessible high-throughput phenotyping tools, and a flexible and dynamic infrastructure for storing and sharing large phenotypic data sets. They also say that effective interdisciplinary communication and cross-disciplinary training will be key for developing a stronger community of biologists who focus on integrating the distinct facets of whole-organism biology.

High-resolution phenotyping

UCD SRP researchers are advancing organism-level research, by exposing vertebrates to environmental contaminants during critical periods of development and adult life, and then studying how this exposure affects complex physiological and behavioral phenotypes, as well as the overall health of the organisms. One method they use for high-resolution molecular phenotyping is quantitative proteomics, which provides information about all the proteins in a sample.

In the [Kültz lab](#), investigators use certain fish as vertebrate models for this research. Fish have less complex life histories, can be more readily monitored than many mammals, and are often naturally exposed to contaminants that are relevant to humans.

“Dissection of complex phenotypes, at high spatiotemporal resolution, represents an enormous task,” Kültz said. “High-throughput phenotyping technology, such as metabolomics, proteomics, or imaging-based technologies, are being pushed to new limits, and new tracking technologies using miniaturized sensors are now being developed to enable environmental monitoring in more natural contexts.”

Citation: Kültz D, Clayton DF, Robinson GE, Albertson C, Carey HV, Cummings ME, Dewar K, Edwards SV, Hofmann HA, Gross LJ, Kingsolver JG, Meaney MJ, Schlinger BA, Shingleton AW, Sokolowski MB, Somero GN, Stanzione DC, Todgham AE. 2013. New Frontiers for Organismal Biology. *Bioscience* 63(6):464-471.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

[Return to Table of Contents](#)


Critical gaps in household air pollution research identified



By Paula Whitacre

Household air pollution (HAP) from smoky, inefficient traditional stoves used for cooking and heating affects nearly 3 billion people, almost half the world's population. HAP is the leading environmental cause of death and disability in the world today. Yet, significant research gaps persist about the health effects of these stoves and the solid fuels used in them, and the impacts of alternatives, according to a June PLOS Medicine [article](#) authored by a group of researchers that included NIEHS Senior Advisor for Public Health John Balbus, M.D.

William Martin, M.D., associate director for prevention research and health promotion at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), served as the lead author.

“The real research gap that must be addressed is whether clean stoves and clean fuels really work,” he said during a podcast discussion about the findings, hosted by NICHD in June.



Linked audio
[Listen as Glass interviews guests about the health problems posed by indoor air pollution \(24:03\)](#)
[Transcript](#) (Launches in new window)
Download Media Player:  Quicktime 

Development of the article's findings and conclusions began with a May 2011 [workshop](#), Health Burden of Indoor Air Pollution on Women and Children in Developing Countries, spearheaded by NIEHS, NICHD, and the Fogarty International Center (FIC). Research gaps were identified in seven disease areas — cancer, infections, cardiovascular disease, burns, ocular disorders, respiratory disease, and maternal, neonatal, and child health. In addition, four cross-cutting areas were found to merit further research — exposure and biomarker assessment, women's empowerment, behavioral approaches, and program evaluation.

During the podcast, Balbus focused on the area of exposure and biomarker assessment.

“More studies, especially using more sophisticated methods, are needed to get a really accurate idea of how clean cookstoves need to be,” he said.

Balbus noted that the variability in conditions — ranging from the type and wetness of fuel used and the way people move around their homes, to the way the homes are constructed and ventilated — poses a challenge to research. The NIEHS Exposure Biology Research Program is currently promoting the development of a new generation of exposure monitors to overcome these challenges.



Balbus is the NIEHS lead for global environmental health. (Photo courtesy of Steve McCaw)

Findings align with clean cookstove initiative

The researchers hope their work will contribute to successful achievement of the goal of the [Global Alliance for Clean Cookstoves](#) — for 100 million homes to adopt clean and efficient cookstoves and fuels by 2020.

“We recommend approaches that include everything from birth cohort studies, to randomized controlled trials, to perhaps even more timely program evaluation of the major implementation studies around the world,” Martin said. “As a research community, we need to partner with these implementers to work together.”

“It’s not just a matter of buying cleaner, more efficient cookstoves and giving them to people who need them,” agreed Roger Glass, M.D., Ph.D., FIC director and another author of the article, during the podcast. “If we in the developed world really want to help, then we must conduct the necessary research as to what is acceptable and what really works to reduce exposures and improve health.”

Yvonne Njage, M.D., co-organizer of the May 2011 workshop, also participated in the podcast. She noted her personal experience of growing up in Kenya with an indoor cooking fire, which created HAP smoke. She stressed the need to find creative ways to sell the cookstove concept, because of a variety of food and cultural preferences.

“Just because the stove is good in the lab,” she said, “does not mean the women will use it.”

Citation: [Martin WJ 2nd](#), [Glass RI](#), [Araj H](#), [Balbus J](#), [Collins FS](#), [Curtis S](#), [Diette GB](#), [Elwood WN](#), [Falk H](#), [Hibbard PL](#), [Keown SE](#), [Mehta S](#), [Patrick E](#), [Rosenbaum J](#), [Sapkota A](#), [Tolunay HE](#), [Bruce NG](#). 2013. Household air pollution in low- and middle-income countries: health risks and research priorities. *PLoS Med* 10(6):e1001455.

(Paula Whitacre is a contract writer with the NIEHS office in Bethesda, Md.)

[Return to Table of Contents](#)



Newly appointed to lead the The Ohio State University College of Public Health ([see story](#)), Martin was a member of the NIEHS leadership team from 2006 to 2008, serving as associate director for translational research. (Photo courtesy of Steve McCaw)



Glass heads FIC, the NIH center specifically charged with supporting and facilitating global health research conducted by U.S. and international investigators, building partnerships between health research institutions in the U.S. and abroad, and training the next generation of scientists to address global health needs. (Photo courtesy of NIH)

Workshop addresses contaminants of emerging concern in drinking water


By Paula Whitacre

Professionals from large city water utilities, representing more than 15 million customers, came together with public health researchers, federal regulators, the medical community, and communication experts at a workshop July 10-11 in Washington, DC, to discuss issues associated with contaminants of emerging concern (CECs) in drinking water.

To provide a common vocabulary for the meeting, CECs were defined as a broad range of unregulated chemical compounds that can be found in water supplies in trace amounts, including pharmaceuticals, personal care products, and endocrine disrupting compounds, among others.


“Water utilities are interested in getting ahead of issues related to CECs,” said NIEHS Toxicology Liaison Christopher Weis, Ph.D. “This meeting was an excellent way to bring utilities, communication specialists, and scientists together to share ideas and concerns.” Weis served as a member of the workshop advisory committee and made a presentation on NIEHS-supported research related to emerging techniques in toxicology.

“The challenges for utilities include how to manage and monitor CECs in drinking water and how to communicate to the public about them in absence of definitive information regarding their risk,” said Alice Fulmer, senior research manager at the [Water Research Foundation](#) (see text box), which organized and sponsored the meeting. “Utilities feel the responsibility falls on them, even though CECs have not been shown to have definite human health effects and there are no regulations to control them.”



Linked video:
[Watch the latest WFR educational video about the CEC nitrosamine \(02:00\)](#)

(Launches in new window)

Download Media Player:  Flash

How utilities provide water to the public varies widely across the country, with a range of sources, treatment methods, distribution systems, and state regulations that supplement those on the federal level, explained Richard Sakaji, Ph.D., a water quality manager with the East Bay Municipal Utility District in Oakland, Calif. Despite this variability, “We all have customers and we need better communications tools to talk about nonregulated compounds.”

David Sedlak, Ph.D., co-director of the Water Center at the University of California, Berkley, noted some of the limitations in risk assessments related to CECs. “Most of the research [on CECs] has been on ecological impact and aquatic ecosystems, rather than human health. Stronger messages require more science,” he observed.



An important topic at the workshop was how water professionals could best communicate with the medical community, particularly pediatricians, about CECs. Discussing strategies during a break are, from left, Leonardo Trasande, M.D., associate professor in pediatrics, environmental medicine, and population health at New York University Langone Medical Center; Jerome Paulson, M.D., director of the Mid-Atlantic Center for Children's Health and the Environment at Children's National Medical Center in Washington, D.C.; and Weis. (Photo by Paula Whitacre)

He also called for more research on transformation and degradation products that could potentially lead to toxic compounds.

Weis highlighted ways NTP can further research related to CECs in water. “Toxicology for the 21st Century (Tox21) is designed to develop methods that help us prioritize compounds to investigate and develop predictive models for biological response in humans,” he said. Acknowledging that Tox21 does not address the exposure component of risk assessment, Weis said, “If a chemical tests positive in many assays and has high exposure nationwide, that’s the kind of prioritization that we might consider working on together.”

The approximately 40 participants identified ways to enhance communication between the water sector, researchers, regulatory agencies, and public health groups, including more organized discussions, publications, and workshops that span across disciplines. For example, several water-sector participants suggested finding ways to work with pediatricians, Centers for Disease Control and Prevention agencies, and other health care professionals on water issues.

“Utilities are eager to sit at the table to provide input about the type of research that would help answer the questions they receive from the public,” Fulmer said. “We are also interested in hearing what kind of work we can do that would help the public health community.”

(Paula Whitacre is a contract writer with the NIEHS office in Bethesda, Md.)

[Return to Table of Contents](#)

ONES awardee honored by Burroughs Wellcome

By Eddy Ball

NIEHS Outstanding New Environmental Scientist (ONES) awardee Vishal Vaidya, Ph.D., is one of five North American scientists selected to receive 2013 Burroughs Wellcome Fund (BWF) Innovation in Regulatory Science Awards.

[Vaidya](#) is an assistant professor of medicine and environmental health at Harvard Medical School and Harvard School of Public Health. He also directs the laboratory of kidney toxicology and regeneration in the renal division of Brigham and Women’s Hospital, with a research emphasis on discovery and evaluation of biomarkers for early detection of kidney injury, and investigating the molecular mechanisms of kidney tissue repair.

Water Research Foundation (WRF)

WRF, which funded the Workshop to Broaden the National Dialogue on Contaminants of Emerging Concern and Public Health, has worked with a variety of professional partners to identify, prioritize, fund, manage, and communicate scientifically sound research across the globe.

The foundation is a nonprofit organization that invests research dollars from more than 950 organizations in the U.S. and abroad, to tackle an array of issues related to the treatment and delivery of clean drinking water. Since 1966, it has managed more than 1,000 high-impact research studies, valued at more than \$500 million. Among the group’s many online resources is an archive of [webcasts](#) about various aspects of drinking water management.



With [grant](#) support from his 2012 NIEHS ONES award ([see story](#)), his group currently studies fibrinogen signaling in kidney tissue repair. The BWF award will give Vaidya's group \$100,000 per year, for the next five years, to map the biology of a toxic kidney cell. His goal is to advance regulatory science, by transforming kidney safety assessment using tools and technologies at the interface of quantitative systems pharmacology.

In a message to NIEHS and NTP Director Linda Birnbaum, Ph.D., about the award, Vaidya credited NIEHS support with helping make the award a reality. "The ONES grant set the ball rolling for me two years back and now I am just having lot of fun in science."

In addition to his ONES award, Vaidya was the recipient of an NIH Pathway to Independence Award, from NIEHS, in 2007 ([see story](#)). He was also a summer intern at NIEHS during graduate school. Vaidya completed postdoctoral training in the renal division of Brigham and Women's Hospital, supported by a grant from the National Kidney Foundation, in 2005, prior to his faculty appointments at Harvard.

Vaidya is an active member of the Society of Toxicology (SOT) and the recipient of a number of SOT awards. In 2012, he received the group's American Scientist of Indian Origin Young Investigator Award.

According to the BWF website, the [Innovation in Regulatory Science Awards](#) provide up to \$500,000, over five years, to academic investigators who are addressing research questions that will lead to innovation in regulatory science, with ultimate translation of those results into improving the regulatory process. These awards are intended to provide support for academic researchers developing new methodologies or innovative approaches in regulatory science that will ultimately inform the regulatory decisions the U.S. Food and Drug Administration and others make.

[Return to Table of Contents](#)

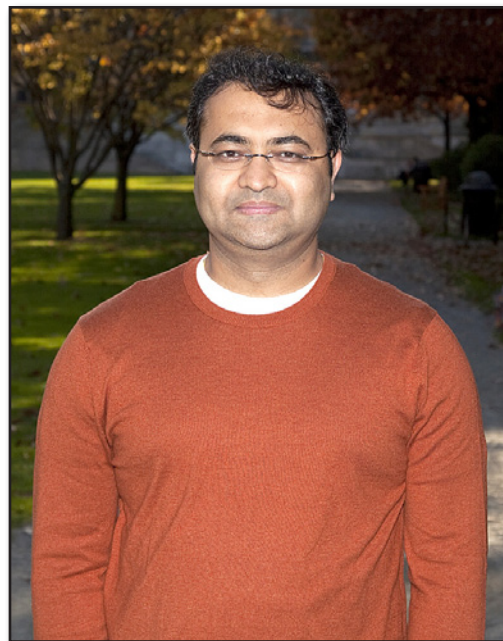
Grantee Gary Miller named ToxSci editor-in-chief

By Eddy Ball

The Society of Toxicology (SOT) Board of Publications announced July 23 the selection of NIEHS grantee [Gary Miller, Ph.D.](#), as editor in chief of [Toxicological Sciences](#). According to Board of Publications Chair Janice Chambers, Ph.D., Miller was chosen from a group of highly qualified SOT members to lead the flagship journal and will officially assume his new duties Sept. 1.

"We look forward to his vision and enthusiasm, as he initiates his leadership of the journal and continues ToxSci's rise in prestige and significance to the toxicology community," Chambers wrote in the announcement.

According to the journal's website, the mission of Toxicological Sciences, the official journal of the [Society of Toxicology](#), is to publish premier peer-reviewed, hypothesis-driven, original research in all areas of toxicology. The journal has a five-year impact factor of 4.836.



Vaidya's research reaches across several biomedical specialties. Along with his other appointments, he also leads the Regulatory Sciences program in systems toxicology in the [Harvard Program in Therapeutic Science](#). (Photo courtesy of Vishal Vaidya)

“Some of the best research published in ToxSci has been supported by NIEHS and other organizations concerned with the contributions of toxicology to public health,” Miller said. “I expect that this will continue, and I look forward to reviewing more outstanding research of this kind.”

A leader in his field

NIEHS Division of Extramural Research and Training Director Gwen Collman, Ph.D., welcomed the news of Miller’s appointment. “Gary has established one of the top programs we fund in the area of neurodegenerative disease,” she said. “It’s very gratifying to see that his groundbreaking work in toxicology is being recognized in a way that will strengthen his influence on the field.”

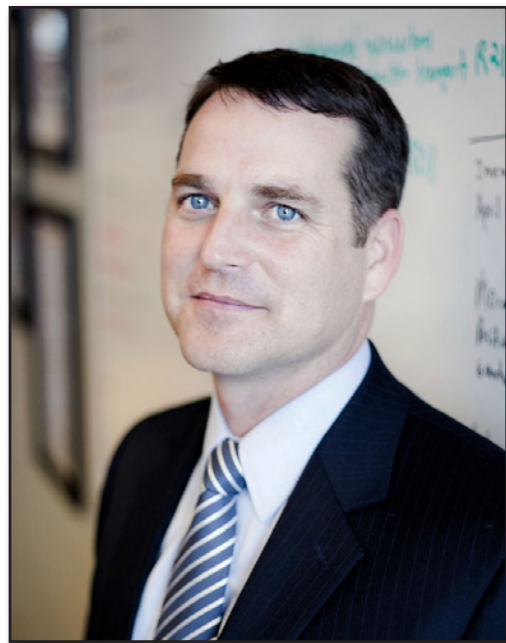
Miller is the Asa Griggs Candler Professor of Environmental Health and associate dean for research in the Rollins School of Public Health at Emory University, and lead of the NIEHS-funded [Emory Parkinson’s Disease Collaborative Environmental Research Center](#). Miller received the 2010 SOT Achievement Award for his significant early career contributions to toxicology. In 2012, he was named [Georgia Research Alliance \(GRA\) Distinguished Investigator](#), one of only six scientists so honored in GRA’s 22-year history.

In addition to his existing grants, Miller will direct the new HERCULES (Health and Exposome Research Center at Emory) program, an Environmental Health Sciences Core Center. Miller’s emphasis on the [exposome](#) is potentially transformative — as well as ambitious — as it refers to the quantifiable and cumulative set of environmental influences and biological responses throughout the lifespan.


Miller’s laboratory focuses on the role of environmental and genetic factors involved in neurological disease, with an emphasis on regulation of monoamines. His group has developed a mouse model of Parkinson’s disease that displays progressive loss of dopamine neurons and a variety of early-stage motor and non-motor symptoms of the disease, providing new insights into therapeutic strategies ([see story](#)).

Overseeing Miller’s [grants](#) in the Division of Extramural Research and Training are Cellular, Organ, and Systems Pathobiology Acting Branch Chief Cindy Lawler, Ph.D., and program administrators Les Reinlib, Ph.D., Sri Nadadur, Ph.D., and Carol Shreffler, Ph.D.

[Return to Table of Contents](#)




Toxicological Sciences Editor-in-Chief Gary Miller (Photo courtesy of Gary Miller)



Linked video:
[Watch as Miller discusses the critical role the environment plays in human health \(02:00\)](#)

(Launches in new window)

Download Media Player:  Flash [↗](#)

Martin named dean of Ohio State University College of Public Health

By Eddy Ball

In August, former NIEHS Associate Director William Martin, M.D., begins a new phase in his career as dean of the Ohio State University College of Public Health, the university announced June 14 in a press release.

During his tenure at NIEHS from 2006 to 2008, Martin served as director of the Office of Translational Research, where he led the Head-off Environmental Asthma in Louisiana (HEAL) study of asthma outcomes in children in post-Katrina New Orleans.

Along with his work with the HEAL study, Martin oversaw technology transfer at NIEHS; helped advance the journal *Environmental Health Perspectives*; and represented the Institute at several global environmental health forums, such as the U.S.-Japan Gene, Environment, and Disease Panel. Martin also played a part in making the NIEHS Clinical Research Unit a reality in 2007.

Following his tenure at NIEHS, Martin assumed the position of associate director for disease prevention and health promotion at the Eunice Kennedy Shriver National Institute of Child Health and Human Development at NIH. He continued to be instrumental in global environmental health efforts and, with NIEHS Senior Advisor for Public Health John Balbus, M.D., and Fogarty International Center Director Roger Glass, M.D., Ph.D., was an NIH lead on the Global Alliance for Clean Cookstoves initiative.

For Martin, the new position is sort of a coming home again experience, both geographically and professionally. With his training in pulmonary medicine, Martin always had an eye toward the clinical applications of basic research. Prior to joining NIEHS, he had risen through the ranks to the position of dean of the College of Medicine at the University of Cincinnati. Before moving south, he held faculty positions at the Mayo Clinic in Minnesota and at the Indiana University School of Medicine.

[Return to Table of Contents](#)



Martin in his office at NIEHS (Photo courtesy of Steve McCaw)

Superfund pilots new promotora training module in Mexico and Arizona

By Sarah Wilkinson

The NIEHS-funded University of Arizona Superfund Research Program (UA SRP) and Dean Carter Binalational Center for Environmental Health Sciences piloted another module, this summer, in the series “Transferable Training Modules on Environmental Science.” The new module, “Health Risks from Environmental Exposures,” covers topics such as everyday risks, dose response, hazard consequences, and biological variability.

Funding for this chapter of the modules was provided by the UA SRP and leveraged with a Community Connections grant from the University of Arizona Foundation. The risk module was developed collaboratively by promotoras working for the Sonora Environmental Research Institute Inc. (SERI) in Tucson, Ariz., and [Denise Moreno Ramírez](#), coordinator of the UA SRP Community Engagement Core. UA SRP researcher [Miranda Loh, Sc.D.](#), was the expert advisor on the project.

Health advocates provide outreach to the community

Like the other modules in the series, the risk module was developed for use by *promotoras de salud*, or Latina community health advocates. Promotoras are peer educators who receive specialized training to promote healthy living in their communities, and are a proven method of information transfer, especially within disadvantaged populations. They act as conduits of information between their community and an institution or organization. Because they share a language and a culture with their audience, promotoras are able to provide information in a relevant and accessible manner.

The transferrable training modules are based on a train-the-trainer model. This model is based on providing training to promotoras, who in turn transfer the knowledge gained to other promotoras, and subsequently to their communities at large. Each module is comprised of background information, a PowerPoint presentation, hands-on activity ideas, additional resources, and instructional materials to guide promotoras in the development and implementation of interactive trainings.

The flexible nature of the modules allows for replication and adaptation of the trainings. While the core information remains the same, examples and activities can be modified to fit unique audiences, such as various communities, government agencies, businesses interested in greening their practices, and primary, secondary, and collegiate education, including tribal colleges.



Shown, from left, are SERI promotoras Vazquez, Maria Luisa Morales, and Florecita Morales who joined Ramirez, as the training got underway in Naco. (Photo Courtesy of Tom Carlson)



Hands-on activities demonstrated important concepts about exposure routes, such as the hazards of placing household chemicals in unmarked containers. (Photo courtesy of Denise Moreno Ramirez)



SERI promotoras, center, delivered an interactive presentation, with plenty of time for questions from community participants. (Photo courtesy of Denise Moreno Ramirez)

Testing the program on the ground in Mexico

Ramírez, Loh, and SERI promotoras Maria Luisa Morales, Florecita Morales, and Susana Vazquez travelled June 19 to the Naco Wellness Initiative's Casas Saludables clinic in Naco, Sonora, Mexico, to pilot test the new module and to present an existing module on pesticides. The SERI promotoras led a group that included representatives from Casas Saludables, Naco Library, Mexican Red Cross, Municipal Civil Protection, and Naco Fire Fighters, through a presentation and hands-on activities.

Tom Carlson, president of the Naco Wellness Initiative, was very pleased with the training, and spoke of the benefits it brought to his program. "Everyone loved all of the special attention you gave, from the workshop itself to the snacks and prizes, and especially your friendship. We will be working the materials into our community health education programming," he said.

While in Naco, the group from Tucson also had the opportunity to provide a special radio interview with Vicente Borquez López, director of the border region radio station Radio Cultural Stereo 106.9 FM, allowing community listeners from the sister cities of Naco and Bisbee, Ariz., to learn about the endeavor.

Carlson said he looks forward to additional opportunities for collaboration. "I know that we can find opportunities to work together that will be of great benefit to the services of the clinic and to the people of Naco. There is such need for additional medical attention and health education programs for both young and old, and we would love to partner with you as we go about reaching out to those people."

Once finalized, the "Health Risks from Environmental Exposures" module will be available in English and Spanish on the UA SRP and Binational Center websites for free download, along with the [currently available modules](#).

(Sarah Wilkinson, Ph.D., is the UA SRP research translation core coordinator. She writes and edits the UA [SRP News and Highlights](#), where this story first appeared.)



During a radio interview at 106.9 FM, from left, radio station director López interviewed SERI promotoras Florecita Morales and Maria Luisa Morales, Casa Saludables president Lupita Sánchez, and UA SRP lead researcher Loh. (Photo courtesy of Denise Moreno Ramírez)



Instructors and participants at the training in Naco (Photo courtesy of Tom Carlson)



In Tucson, participants used swabs to test for lead in the type of pottery commonly found in homes in the border region. (Photo courtesy of Denise Moreno Ramírez)

Back in Tucson for fine tuning

Closer to home, the team held another pilot training July 11 in Tucson. The audience was comprised of volunteer promotoras at SERI. Maria Luisa Morales and Florecita Morales delivered the “Risk Assessment from Environmental Exposures” presentation, while Vazquez led the hands-on activities.

At the end of the training, participants provided input on the content of the information they received, as well as the format of the training. Their responses were captured using hand-held response devices, or clickers, and polling software. Use of the clickers let individuals provide answers anonymously, while the aggregate responses of the group were instantaneously projected on screen. In addition, the participants gave written feedback on improvements for the module, which will be incorporated into the final version.

After the survey, participants were quizzed about what they had learned about risk assessment, by having them select a topic and answering a question. Trainers were able to discuss the answers with participants, and to revisit the information immediately, making the training more effective. It also made it more fun. As Ramírez explained, “It was a lot less scary for the promotoras than the usual pre- and post-test knowledge surveys.”

For additional information about UA SRP programs for community-based outreach training in border communities, visit these sites:

[Transferable Training Modules Targeting Promotoras](#)

[Bilingual Environmental Science Modules for Communities Available](#)

[Return to Table of Contents](#)

Migrant farmworker housing fails to provide relief from heat

By Nancy Lamontagne

After working all day in extreme heat, migrant farmworkers continue to feel the effects of dangerous heat and humidity throughout the night, according to a new NIEHS-funded [study](#). Researchers led by [Sara Quandt, Ph.D.](#), from Wake Forest School of Medicine reported the new findings, which have implications for worker safety and health.

“Migrant workers have a unique situation because their housing is usually provided by the employer,” Quandt said. “Although some farmworker housing in North Carolina is exemplary, that is really the exception. Most housing is so crowded and of such poor quality that it is nearly impossible to get cool at night.”



In response to concerns from North Carolina organizations and clinics that serve migrant farmworkers, Quandt's research team studied the heat index in farmworker housing. (Photo courtesy of Sara Quandt)

The new study is part of a larger community-based participatory research project examining the relationship between farmworker housing and health. The researchers have been conducting research with farmworkers since 1996, working with many North Carolina organizations and clinics that serve farmworkers, including the North Carolina Farmworkers Project in Benson and Student Action with Farmworkers in Durham. These community partners brought their concerns about the heat in farmworker housing to Quandt's research.

Housing assessment

The researchers responded to the concerns by assessing the evening heat index in 170 common rooms and 316 sleeping rooms at 170 North Carolina migrant farmworker camps during the summer.

They found that many of the farmworker camps had windows that didn't open or lacked screens to keep out insects if they did open. More than three-quarters of the common rooms (134, 79.8 percent) and more than half of the sleeping rooms (187; 60.7 percent) had no air conditioning. Electric fans were used in many of the sleeping rooms (248; 78.5 percent). Most heat index measurements — 89 percent in common rooms and 81 percent in sleeping rooms — exceeded the danger threshold of 80 degrees Fahrenheit, combined with at least 40 percent relative humidity.

Health and policy implications

“The combination of high heat and humidity impairs sleep quality, and if the farmworkers can't recover from the heat they experience during the day, they may be more at risk for on-the-job injuries,” Quandt said. “Also, the high heat index can worsen any dehydration they may be experiencing.”

Dehydration can be a significant problem for the farmworkers, especially because many of them are drinking contaminated water. A [study](#) published by the researchers last year reported that drinking water from all 181 farmworker camps they visited contained total coliform bacteria, and 34 percent of the camps had total coliform levels higher than those allowed by U.S. Environmental Protection Agency water standards.

The researchers are now working with their community partners to craft policy briefs that can be used to educate policymakers at local, state, and national levels about the research findings and issues related to the dangerous evening heat indexes in farmworker housing.



It can be challenging to get cool inside farmworker housing, because of crowded conditions. North Carolina has no heat standards that mandate rest or water breaks for farmworkers, and federal standards for farmworker housing do not include requirements for air conditioning or other cooling methods. (Photo courtesy of Sara Quandt)

Citation: [Quandt SA, Wiggins MF, Chen H, Bischoff WE, Arcury TA](#). 2013. Heat index in migrant farmworker housing: implications for rest and recovery from work-related heat stress. *Am J Public Health* 103(8):e24-e26.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

[Return to Table of Contents](#)

Duke workshop addresses environmental justice issues in North Carolina

By Sara Mishamandani

Environmental justice, exposure to toxic chemicals, and sustainability were topics of discussion at the [Environmental Justice Workshop](#) June 28-30 in Durham, N.C., hosted by the NIEHS-funded Duke University Superfund Research Program (SRP).

Faculty and students from [Johnson C. Smith University](#), an historically black institution in Charlotte, N.C.; Charlotte-Mecklenburg K-12 teachers; and Charlotte-area community leaders met with scientists, learned about environmental health topics, and explored connections between environmental justice and sustainability.

Eileen Thorsos, of the Duke SRP Research Translation Core, organized the event and kicked off the meeting with a case study to explore definitions for, and connections between, environmental justice and sustainability. The workshop also included a tour of [SEEDS](#), an urban garden in Durham that provides a variety of programs to local youth and community members, and a visit to the Rogers-Eubanks neighborhood ([see text box](#)), an historically African-American community with a long history of battling environmental injustice.

“Our workshop brought SRP research on health risks from toxic exposures into context and connected it with the experiences of communities organizing against environmental injustices,” said Thorsos. “Our teachers, community leaders, and students are taking these connections between research, environmental justice, and sustainability, back to their classrooms and communities.”

Linking chemical exposures to health

The workshop included talks by local scientists on environmental health topics relevant to environmental justice. Rebecca Fry, Ph.D., an NIEHS-funded University of North Carolina at Chapel Hill SRP investigator, explained how arsenic poisons the water of individuals around the globe, including North Carolina. Her research investigates certain pathways and altered genes associated with arsenic exposure. By understanding these molecular pathways, scientists can accurately detect exposure, predict individual differences in susceptibility to disease, and understand the molecular basis for disease.



Environmental Justice Workshop participants visit the Rogers Road neighborhood in Orange County, N.C. Community organizers have lobbied against a nearby landfill for 25 years. The landfill closed to residential waste the day participants visited. (Photo courtesy of Noelle Wyman)



Fry discussed the links between biological pathways and long-term human health effects of heavy metals. (Photo courtesy of Rebecca Fry)

Christine Ekenga, Ph.D., an NIEHS postdoctoral fellow, briefed participants on the role of epidemiology in promoting and protecting public health, and described how epidemiology is used to study the relationship between chemical and nonchemical stressors and human health outcomes.

Heileen Hsu-Kim, Ph.D., a Duke SRP scientist, focused on an activity for teachers to bring back to their classrooms called NanoToss, a felt board activity that helps K-12 students conceptualize how coatings on nanomaterials affect their mobility in the environment. She also described the concepts of nanoremediation and bioremediation to clean up the environment. Hsu-Kim's NIEHS-funded project investigates the use of nanomaterials to treat sediment and water contaminated by developmental toxicants, boosting microbial degradation of the contaminants.

Anthony Oliveri, a Duke SRP trainee, also led the participants on a tour of the Duke Neural and Behavioral Toxicity Assessment Core, where Duke SRP research connects toxic exposures to changes in emotion and behavior.



Ekenga studies urban pollutants that influence hormones in the human body and their connection with breast cancer. (Photo courtesy of Steve McCaw)

Engaging children in farm worker justice and sustainable agriculture

Teachers, faculty, and students attending the workshop gained valuable insight into ways to teach children about farm workers, food and farming, and cultural awareness from Leanne Simon, a multimedia journalist and author. Participants also met with people from [Student Action with Farmworkers](#), to learn about their work in the Southeast to create a more just agricultural system, and went on a tour of [Fickle Creek Farm](#) to learn about how they integrate multiple sustainable farming practices.

“We are very excited about teaching our students about harvesting fruits and vegetables, pesticides, and immigrant farmworkers,” said Lara Harris, a Charlotte-Mecklenburg Schools literacy specialist and workshop participant. “Working with community members who attended the workshop, we are also planning to plant a community garden with Charlotte-Mecklenburg students, so they will have the opportunity to connect what they learn in school to real-world experiences.”



Felicia Walker-Cooper, a Charlotte-Mecklenburg Schools instructional literacy coach, smells lemon balm at SEEDS, which promotes leadership development among inner-city high school students through urban gardening. (Photo courtesy of Noelle Wyman)

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

The environmental justice struggle in the Rogers-Eubanks neighborhood

The [Orange County Landfill](#), located on Eubanks Road in Chapel Hill, N.C., has operated since 1972, when Mayor Howard Lee promised improved infrastructure and benefits to the community, including parks and recreational facilities, street lamps, and public water access, in exchange for housing the county landfill. The landfill did not have restrictions and was built without a liner, putting its contents, including hazardous materials, such as chemical waste, paint, and batteries, in direct contact with soil and groundwater.

Ten years later, instead of closing down as originally promised, the landfill was expanded to meet waste storage demands of a growing county. Contaminated surface, ground, and well water affected some community members who did not have access to public drinking water, and litter was blown off trucks heading to the landfill, scattering across lawns and roadsides.

As promises to the community remained unfulfilled, neighbors organized to bring awareness to the injustice imposed on their community. After more than 40 years of enduring the landfill, David Caldwell, of the Rogers-Eubanks Neighborhood Association (RENA) and Coalition to End Environmental Racism, won a small victory. As of June 30, the Orange County Landfill no longer accepts household waste.

The Duke Environmental Justice Workshop participants joined David Caldwell and other members of RENA June 29 to witness the closure ceremony. Despite this win, the landfill will remain in operation and continue to accept tires, scrap metal, large appliances, electronics, and other hazardous wastes.

[Return to Table of Contents](#)

LMG fellow begins independent career in Israel

By Monica Frazier

Former NIEHS Laboratory of Molecular Genetics (LMG) postdoc Shay Covo, Ph.D., began a new career in June as an assistant professor at [The Hebrew University of Jerusalem \(HUJ\)](#) in Israel.

Covo will create his laboratory in the Department of Plant Pathology and Microbiology and work among the Faculty of Agriculture, Food, and Environmental Quality Sciences located in Rehovot. Covo will be comfortable in his new location, near the Weizmann Institute of Science where he completed his Ph.D. research on double-strand breaks and repair of lesions in DNA.

Transitioning from postdoc to lead researcher

While a member of the Chromosome Stability Group, led by lead researcher [Michael Resnick, Ph.D.](#), Covo worked on defects in sister chromatid cohesion and genome instability in yeast.



Covo also shared his passion for science with high school students, during North Carolina DNA Day ([see story](#)). He was known, among colleagues, for his delightful sense of humor. (Photo courtesy of Steve McCaw)

“Shay had unique and creative insights that led to the development of new concepts about the role of sister chromatids in protection against genome change. He was a continual source of ideas, a welcome critic, and a wonderful colleague and collaborator with other members of the lab,” Resnick said.

At HUJ, Covo will focus his group’s study on genome instability in plant pathogens, and will continue his work with yeast, to address mechanisms that maintain genome stability normally and in response to environmental challenges.

Covo was known among the members of LMG for his many useful comments during seminars. Resnick added that, in addition to Covo’s broad research interests, his ability to encourage and teach trainees, including high school students, in the lab, were among the traits that would lead to his success as a mentor.

“Shay is a natural-born researcher and teacher, showing tremendous patience, diligence, and passion for each project,” Resnick noted.

Finding your niche

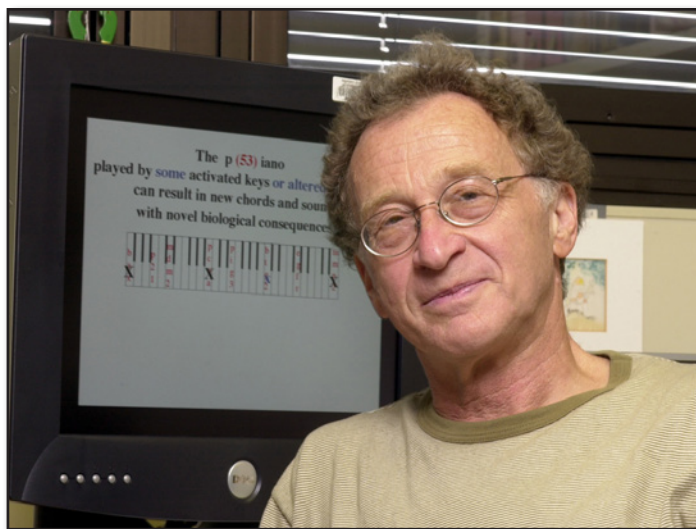
NIEHS attracted Covo as the perfect place to carry out his postdoctoral research, because of his interest in DNA repair, and the many experts in the field whose work he was already familiar with, including Resnick. However, the benefits of NIEHS went far beyond mastering technical skills.

Covo described participation in the LMG seminar series and retreats as some of the most beneficial experiences he had while at NIEHS. Most importantly, he credited the unique viewpoint he adopted on molecular and cellular processes while at NIEHS with preparing him for taking on his own laboratory.

Covo encouraged other trainees to be creative with their research interests, and to try to find their own niche. He commented, “I thought that after so many years of research, I was fixed on a specific direction, but I was able to twist my research program into a completely different direction.”

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)

[Return to Table of Contents](#)



Mentor Resnick (Photo courtesy of Steve McCaw)

Linked audio:

[Listen to an interview with Resnick about his group's research that found a link between DNA damage and immune response \(02:31\)](#)

(Launches in new window)

Download Media Player: Quicktime

Research is generational for Falk grandson

By Robin Arnette

Under the guidance of Institute scientists and staff, the National Institutes of Health (NIH) [Summer Internship Program \(SIP\)](#) at NIEHS allows talented high school, undergraduate, and graduate students to engage in their own research projects. All 34 participants in this year's program were excited about the summer and quickly settled into the routine of research, workshops, and seminars. For one of them, taking part in these activities had special meaning, simply because of his last name.

Summer intern Michael Falk is the grandson of the late Hans Falk, Ph.D., the Institute's first scientific director and one of the first scientists to join NIEHS in 1967 (see text box). Michael is forging his own research path, by working out a bioinformatics strategy as part of the Mouse Methylome Project, a study cofunded by NTP and the NIEHS Division of Intramural Research, to discover which regions of DNA are involved in the development of spontaneous liver tumors in a particular strain of mice.

Paul Wade, Ph.D., of the Laboratory of Molecular Carcinogenesis, and Alex Merrick, Ph.D., of the NTP, head the Mouse Methylome Project. Pierre Bushel, Ph.D., of the Biostatistics Branch and David Fargo, Ph.D., of the Integrative Bioinformatics Group, serve as Michael's co-mentors. They both believe Michael's involvement in the working group is a good opportunity for him to learn about big data.

Geared toward science

Michael was born in Connecticut, and grew up in Atlanta, where he graduated from high school in May 2012 with a college preparatory (International Baccalaureate) diploma with distinction. He entered the Georgia Institute of Technology with the intention of getting a degree in materials science and engineering, but midway through the semester, his thinking changed. He wondered whether bioinformatics would be a better fit. He had always enjoyed playing computer games and had taken courses in MATLAB and JAVA, two high-level programming languages. All he needed was a chance to delve into his burgeoning interests.

"I looked around for a summer research project involving big data and found what I was looking for at NIEHS," Michael said.

Using big data to tackle a big problem

Bushel said the Mouse Methylome Project began after NTP researchers noticed the C3H strain of mice exhibited an historically high incidence of spontaneous liver tumors compared to other strains.

Helping to shape NIEHS

During his tenure at NIEHS, Hans Falk made significant contributions to the field of environmental health sciences, such as founding one of the first health hazard assessment groups to evaluate chemical exposure risks, and establishing the listing of chemicals entered into the first NTP Report on Carcinogens. As an expert in chemical carcinogenesis, he authored more than 100 peer-reviewed journal articles on the topic. Falk passed away in 1985, but his legacy of scientific excellence remains the standard at the Institute. One of the longest running lecture series at NIEHS bears his name.



Summer intern Michael Falk said he believes big data challenges in genomics require the talents of researchers from the computer sciences as well as from the life sciences. (Photo courtesy of Steve McCaw)

They theorized that this variable incidence of liver cancer may be due, in part, to differences in epigenetic machinery and the level of DNA methylation in and around critical tumor suppressor genes.

Michael's goal was to determine which regions of DNA were differentially methylated. Since it involved so much data, he used only 2 out of the 19 mouse autosomal chromosomes to make the project easily manageable. Even so, it was still a lot of data.

"You have to have certain skills to be able to manage very complicated and large data sets, and Michael has been able to digest it all fairly well," Bushel said. "He's bright and pretty savvy with different computing environments."

Fargo said the team is only beginning to understand all of the mechanisms that lead to tumor development in these mice, and agreed that Michael is helping to lay the groundwork for the problem.

"In essence, it's an undiscovered continent of things that can be investigated in the data," Fargo added. "We have the potential to unearth several new projects from it."

The tradition continues

Michael never got the chance to meet his grandfather, but Hans Falk's influence may still be seen in members of the Falk family, who are involved in science in some way. Michael said growing up in that environment probably helped shape his trajectory toward the sciences. He said one of the things he will take away from his research experience at NIEHS is confirmation of his earlier hunch — his new major will be computer science.

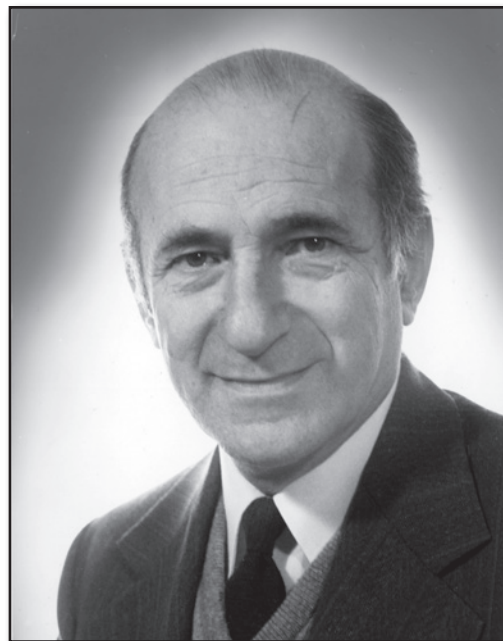
[Return to Table of Contents](#)

Intern-led research takes center stage at 2013 summer poster session

By Ian Thomas

Following a rigorous three months of seminars, workshops, career panels, and research training, the 2013 [NIH Summer Internship Program \(SIP\)](#) at NIEHS drew to a close July 25 with the annual poster session. Held in Rodbell Auditorium, this three-hour event offered students the chance to showcase their newfound research skills, and discuss their work with colleagues and peers.

"It's always a thrill for our staff to walk the aisles at this event and see the incredible work that these kids produce after just a summer of training," said NIEHS Radiation Safety Officer Bill Fitzgerald, during the day's closing remarks.



*Hans Falk at work in an undated photo
(Photo courtesy of Gabrielle Falk)*

2013 Poster Winners

- Top High School Poster — **Forrest Ashworth**, a graduate of the North Carolina School of Science and Mathematics — Ashworth F, de Marchena, J, Jensen P. 2013. Isolating the Function of Galanin-Expressing Noradrenergic Neurons of the Locus.
- Top College Poster — **Spencer Lacy**, a rising junior at North Carolina State University — Lacy S, House J, Li H, Zeldin D, London S. 2013. Htr4 -/- Mice Exhibit Altered Lung Function Following Bleomycin-Induced Fibrosis.

“These students put in a lot of lab time between the months of May and August — a lot of it on their own hours — and that really shows up in the level of quality research that we see here every year.”

Learning from the bench

The key component of SIP is its commitment to giving students real, hands-on experience in a world-class biomedical research setting, by pairing them with members of the Institute’s intramural research team. Through this mentoring partnership, NIEHS interns learn, firsthand, what it means to conduct experiments and analyze data.

“From day one, they made it clear that it was up to us to step forward and take the initiative to learn,” said John Parker, a senior at Elon University whose poster examined the relationship between spatial environments and hippocampal neuron activity in rodents. “From then on, they put the tools in our hands and taught us what we needed to begin generating our own ideas. As internships go, it truly was a fantastic experience.”

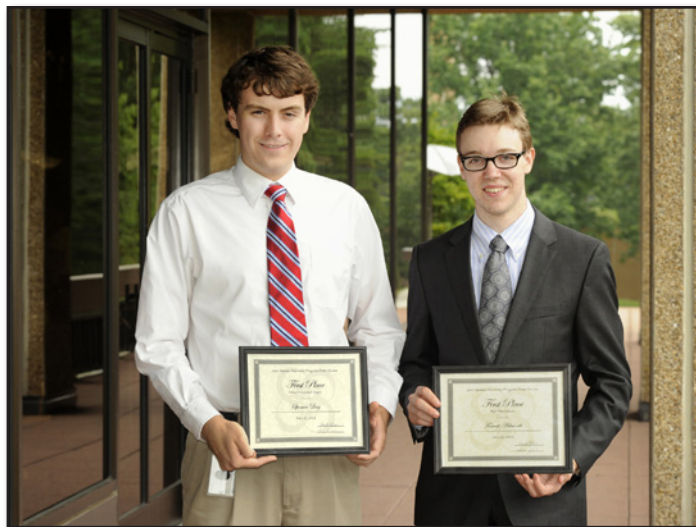
“John was more of a collaborator than a student on this project,” echoed Georgia Alexander, Ph.D., a research fellow in the NIEHS [Synaptic and Developmental Plasticity Group](#) and Parker’s mentor. “Some interns are content to follow their mentor around the lab and simply observe, but he was an active contributor throughout this entire process and that really showed in his poster.”

Keeping in touch

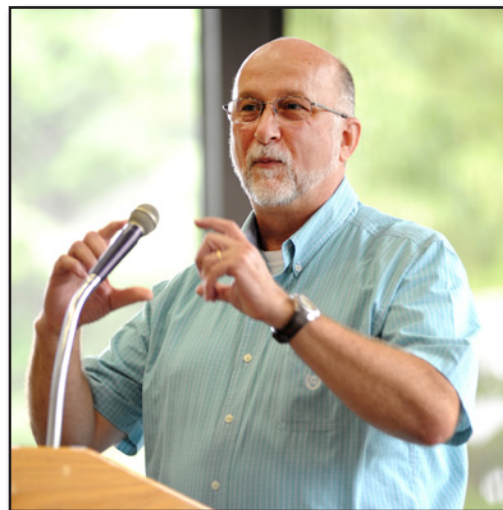
At the conclusion of the event, Fitzgerald announced the winners of the best poster competition, as determined by a panel of NIEHS scientists, and then offered the 2013 SIP class a final word of advice before dismissing them.

“You’ve met some extraordinary people during your time here and, whether it’s through social media or email, you should try to keep in touch with them,” he said. “For all you know, the person sitting beside you today could be your colleague five years from now, or maybe even your boss.”

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)



Lacy, left, and Ashworth accepted their awards for best poster. (Photo courtesy of Steve McCaw)



Fitzgerald congratulated the entire 2013 SIP class. (Photo courtesy of Steve McCaw)



Parker gestured, enthusiastically, as he discussed his poster. (Photo courtesy of Steve McCaw)



*Alexander described her experience with Parker as a collaborative education.
(Photo courtesy of Steve McCaw)*



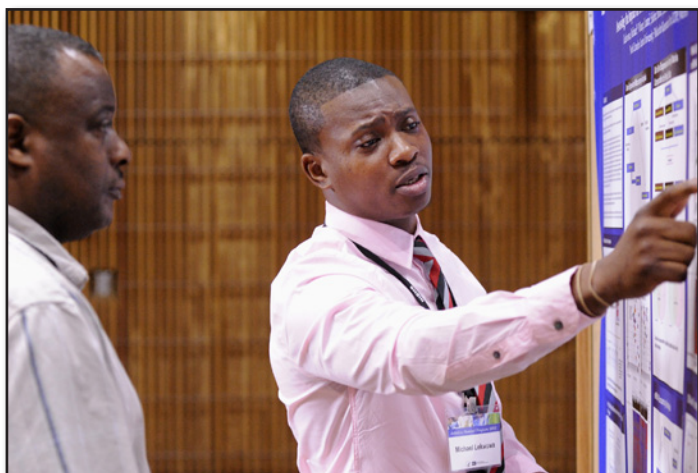
Scholars Connect intern Mia Burks, from St. Augustine's University, discussed her summer project with Huei-Chen Lao, Ph.D., science education and outreach coordinator on detail in the NIEHS [Office of Science Education and Diversity](#). (Photo courtesy of Steve McCaw)



NIEHS and NTP Director Linda Birnbaum, Ph.D., left, enjoyed a laugh with intern Trey Saddler, a rising senior at Salish Kootenai College, and his mentor NTP pathologist Darlene Dixon, D.V.M., Ph.D. (Photo courtesy of Steve McCaw)



*Intern Rachel Hainline, a rising junior at Columbia University, brought some humor to her explanation of the ways DNA precursor concentrations can affect mutagenesis in *E. coli*. (Photo courtesy of Steve McCaw)*



Intern Michael Lekwuwa, a rising senior at North Carolina Central University, returned for his second summer at the NIEHS poster competition. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)

Science Notebook

Bringing down the Tower of Babel in data sharing

By Eddy Ball

As presentations by scientists attending a pair of workshops in June made clear, talking about data sharing is one thing — getting it right is something else entirely.

A workshop co-sponsored by the Office of Scientific Information Management (OSIM) at [NIEHS](#) and the Office of Science Information Management (OSIM) at the U.S. Environmental Protection Agency (EPA) June 25 addressed common language concerns in environmental research, while a two-day meeting June 26-27 at NIEHS addressed operability issues that make the task of integrating databases so challenging ([see related story](#)).

No one mentioned the biblical story of the Tower of Babel during the workshop on Advancing Environmental Health Data Sharing and Analysis: Finding a Common Language, held at the EPA conference center in Research Triangle Park (RTP), N.C. But the difficulty of developing a consistent nomenclature, among the many now in use, to guide searches of multiple databases was the theme of each of the day's ten presentations.

As the directors of NIEHS OSIM, Allen Dearry, Ph.D., and EPA OSIM, Jerry Blancato, Ph.D., explained in opening remarks, the foundation of effective data sharing is achieving standard language for computerized searches of massive data repositories, to make research data funded by the government publicly available. Data sharing, they emphasized, is an outcome that is not only desirable for research and regulatory scientists, but also one mandated by executive order.

"We've come to a new game in town," said Blancato. "We have to have some type of common language."

A common language emerging from a common ontology

Although the workshop substituted several terms that express the idea in plainer language, some presenters lapsed into database shoptalk with a more comprehensive philosophical term, ontology. Ontology refers to the formulation of definitions, classifications, and relationships, using the tools of logic and formal semantics, in order to most effectively achieve the goal of connecting data across different databases, and make these data accessible to standard software tools.

Energizing the push for a common language

While the meeting included a few representatives of databases and data sharing projects elsewhere, the bulk of attendees were people working in the RTP area, representing NIEHS, EPA, the University of North Carolina at Chapel Hill (UNC), RTI International, and North Carolina State University.

This serendipity — the timely coming together of people with a shared interest working within less than an hour's drive of one another — suggested at least one part of a solution for moving common language closer. As part of their efforts to publicize the need for cooperative efforts to build a common language for data sharing, NIEHS Data Scientist Rebecca Boyles noted, concerned scientists can start at home, by getting to know their neighbors, and building a model capable of being replicated and expanded nationwide and even worldwide.

Other suggestions included creating a listserv to extend the conversation, identifying other stakeholders in RTP and elsewhere, investigating other databases with the specific objective of discovering what ontologies they use, and meeting regularly as a group. Several attendees expressed an interest in raising visibility through publications in appropriate journals, such as Environmental Health Perspectives, and trade publications.

Unfortunately, as each of the presenters noted, many databases have emerged independently through good faith efforts to meet discipline-specific needs, using terms that may mean one thing for searches of that database, but something different in other contexts.

EPA Information Management Manager Lynne Petterson, Ph.D., offered a telling example of how this ambiguity might affect environmental health research. The word “flow,” she explained, means something different to atmospheric physicists than it does to hydrologists — a clash of ontologies that reduces the usefulness of information from their respective databases.

The search for solutions

Like several of her co-presenters at the workshop, Petterson is actively involved in developing what she called “a vocabulary for all seasons,” to represent these multiple perspectives, and reconcile past and present meanings of search terms.

Another effort underway at RTI, headed by Carol Hamilton, Ph.D., is developing consensus measures for exposures and biological outcomes, or phenotypes, for use in the NIH Common Data Element Resource Portal, to facilitate genome-wide association studies.

Ontology also has important implications for regulatory science. EPA Acting Chief of the Hazardous Pollutant Assessment Group Lyle Burgoon, Ph.D., described his team’s work developing a semiautomated predictive tool, for inferring the potential hazards to human health from the thousands of chemicals with insufficient toxicologic value data. This is critical, he said, “Because we can’t regulate chemicals with no tox values.”

Next steps

During the concluding session of the workshop, participants split into small groups for discussion. The groups were charged with brainstorming responses to questions about moving the conversation forward among people with interests in broader and more effective data sharing.

Everyone seemed to agree with what North Carolina State University professor and developer of the NIEHS-funded Comparative Toxicogenomics Database, Carolyn Mattingly, Ph.D., said during her presentation, “You need better ways of navigating the data.” The question she and her colleagues faced at the close of the day, however, was just how to gather the momentum for unified progress on a much wider scale ([see text box](#)).



“I didn’t realize we had such good resources just down the road,” observed workshop facilitator Boyles, data scientist with NIEHS OSIM. (Photo courtesy of Steve McCaw)



“What we are doing is part of that larger effort,” Blancato said of the government-wide initiative to improve public access to data. (Photo courtesy of Steve McCaw)



Petterson said her group is striving for an ontology of related-to-ness rather than what-ness. “It [this vocabulary] allows the application to do the work,” she said. (Photo courtesy of Steve McCaw)



Despite the challenges his team is facing in bringing order to billions of chemical and exposure data points, like Petterson, Burgoon remains optimistic about the outcome. “I think this is possible,” he said. “I think this will actually work.” (Photo courtesy of Steve McCaw)



If their smiles are any indication, Dearry, center, and Boyles thought the workshop was meeting its twin objectives of informing people about available resources and motivating the group to redouble its efforts in the quest for a standard ontology. (Photo courtesy of Steve McCaw)



Mattingly identified one major hurdle ahead — convincing database administrators that a common language will benefit them and compensate for the work ahead. “People aren’t interested in data entry,” she said. (Photo courtesy of Steve McCaw)



During the wrap-up session, Jennifer Fostel, Ph.D., NTP scientific administrator of the [Chemical Effects in Biological Systems \(CEBS\)](#) database, set the tone for future collaborations. “We will publish any data you want to publish,” she said. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)

Talking toxicogenomics and global database

By Ernie Hood

The daunting challenges and astonishing opportunities presented by big data are currently attracting attention in many fields, including toxicogenomics, where technology is contributing to rapid expansion in the number and size of databases, most of which do not presently interact effectively. That premise spawned an international meeting at NIEHS June 26-27 titled Workshop on Identifying Opportunities for Global Integration of Toxicogenomics Databases.

More than 30 scientists from around the world, involved with toxicogenomics databases, attended the workshop, which was organized over the past year by Allen Dearry, Ph.D., and Rebecca Boyles, of the [NIEHS Office of Scientific Information Management](#); Jennifer Fostel, Ph.D., NTP scientific administrator of the [Chemical Effects in Biological Systems \(CEBS\)](#) database; and their colleagues Jos Kleinjans, Ph.D., and Diana Hendrickx, Ph.D., from Maastricht University in the Netherlands, who are involved with European Union (EU) toxicogenomics database initiatives.

An array of toxicogenomics databases

The first day of the workshop was devoted to presentations about the many toxicogenomics databases around the world, all of which are somewhat different in their contents and approaches. “It was good for everybody to see the scope of all of the various toxicogenomic databases, as people got some familiarity with the universe of databases that are out there,” said Dearry. “And then the next step is to try to see what we can do to start to enable cross talk between them.”

During the second day of the gathering, the group engaged in discussions designed to yield concrete action plans. Participants identified three types of problems in need of attention — database communication, such as metadata consensus and definition of standards; sustainability, such as funding continuity and data preservation; and the need for education in the field to ensure an adequate and trained future workforce.

First things first

Attendees quickly recognized that, in order to effectively and efficiently tackle such a complex undertaking, solid information about the wants, needs, and goals involved will be necessary prior to moving forward.



“We’ve been a victim of our own success,” Dearry told the workshop audience. “It’s become easier to produce data than it is to store and analyze and disseminate those data. So how can we improve our data management and data handling?” (Photo courtesy of Steve McCaw)



Kleinjans noted the accelerating progress in the field, with rapidly expanding data sets. “What is relevant for all of us is that toxicogenomics, as a technological approach, has not yet stabilized. Sequencing technologies will replace the microarray-based approach we have applied over the last decade or so, and will create an even bigger, a tremendously bigger, data set, which will enable us to go even deeper into the biology.” (Photo courtesy of Steve McCaw)

Boyles posed provocative initial questions to the group about what they expect to gain by interoperability in this field. “This is a lot of time, effort, and, therefore, money, so you’d better be sure that what we’re pursuing is going to add some value to the field.”

With those challenges in mind, step one of the group’s action plan involves research. “The action plan really has some concrete steps in terms of developing our own inventory of what the toxicogenomics databases are, going out and searching for some use cases about toxicogenomics research and how these databases can be useful in that, and then using all of that information to develop a white paper to try to explain what this integration can bring about and why it would be useful to the larger research community,” Boyles explained.

The goal is to have that research accomplished by mid-September, in time for the Research Data Alliance (RDA) [Second Plenary Meeting](#), Building Global Partnerships, Sept. 16-18 at the National Academy of Sciences in Washington, D.C. The RDA is a consortium arrangement among organizations in the U.S., EU, and Australia that aims to accelerate and facilitate research data sharing and exchange. Much of its work is accomplished by its working groups and interest groups, so the intent would be to propose establishment of an RDA special interest group to provide a formal mechanism and framework for enhancing interoperability of toxicogenomics databases.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Weida Tong, Ph.D., director of the FDA Center for Toxicoinformatics, briefed workshop participants on the [MicroArray Quality Control](#) project, the FDA-led, community-wide consortium effort to assess technical performance and application of genomics technologies. (Photo courtesy of Steve McCaw)



Workshop attendees, such as NTP biologist Laura Hall, who took careful notes about the presentations, learned about the nuts and bolts of many different toxicogenomics databases, including large repositories in the U.S., EU, and Japan. (Photo courtesy of Steve McCaw)



Alex Merrick, Ph.D., leader of the Molecular Toxicology and Informatics Group in the NTP Biomolecular Screening Branch, was one of more than 30 workshop participants, who brought a wide range of expertise to the meeting. Merrick joined NTP molecular toxicologist Scott Auerbach, Ph.D., who described the [DrugMatrix](#) database, a large toxicogenomics reference resource. (Photo courtesy of Steve McCaw)



Stephen Edwards, Ph.D., a systems biologist with the EPA National Health and Environmental Effects Research Laboratory, presented an overview of “Toxicogenomics data at the U.S. EPA.” (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)

Exciting developments in Huntington's disease research

By Monica Frazier

The NIEHS Keystone Science Lecture Seminar Series continued June 27 with a lecture by [Cynthia McMurray, Ph.D.](#), offering hope that new findings could eventually lead to novel interventions for treating neurodegenerative diseases and a deeper understanding of the role of environmental exposures in the initiation and progression of these diseases.

McMurray, a senior staff scientist at Lawrence Berkeley National Laboratory (LBNL), spoke to a capacity audience on “Genetics and Metabolic Dysfunction in Huntington’s Disease.”

Funded by NIEHS, McMurray’s group conducts research to identify metabolic markers for mitochondrial dysfunction, working toward a detailed understanding of mitochondria-related diseases and new methods of early detection for triplet expansion disorders such as Huntington’s. Their results and new technologies ([see text box](#)) have the potential to drastically change disease detection and therapy.



McMurray detailed her group’s work during her lecture. (Photo courtesy of Steve McCaw)

**ACS**

Linked audio

[Listen to an interview with authors of the January 2011 Analytical Chemistry feature story on NIMS \(06:54\)](#)

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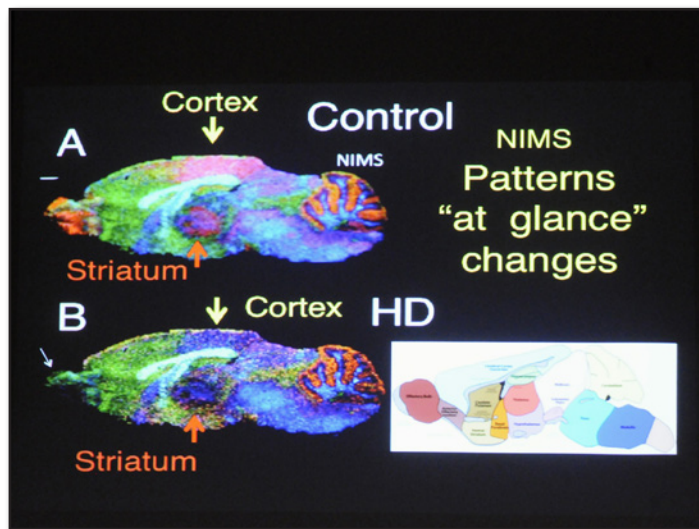
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When normal DNA repair goes wrong

Huntington’s disease (HD), a trinucleotide repeat disorder, results in the progressive neurodegeneration of the brain and death. The disease progression and age of onset are associated with the number of times DNA repair enzymes allow for repeats of the glutamine codon, cytosine-adenine-guanine (CAG).

“One of the most fascinating things about this disease is that DNA repair, which is normally meant to correct our genome, is actually the cause of the mutation,” McMurray said.

The disease begins with an inherited predisposition, but is also dependent on somatic expansion that occurs with age. McMurray’s research group proposed a mechanism for this expansion, which she calls the toxic oxidation cycle, and, for the first time, linked oxidative damage to the mutation that causes HD.



The NIMS technology ([see text box](#)) utilized by McMurray’s research group allows researchers to visualize regional differences in tissue metabolites. (Photo courtesy of Steve McCaw)

A promising implication of McMurray's discovery is the possibility that specific DNA repair enzymes could be targeted to inhibit somatic mutations in the HD gene. The group has already shown that deletion of the gene coding for a key enzyme in the expansion mechanism suppressed the mutation and delayed disease progression in mice, meaning it is possible that, in the future, HD may no longer be a terminal condition.

Widening the therapeutic window

One major goal of researchers has been to develop a therapy to suppress and remove mitochondria-generated oxidative damage in triplet-repeat disorders. A common effort has been to utilize naturally occurring antioxidants, which, as McMurray explained, have been complete clinical failures due to their non-specificity, inability to reach the mitochondria, and poor pharmacokinetics.

McMurray and collaborators have recently developed a set of hybrid synthetic antioxidants that are made up of a mitochondrial-targeting moiety and an antioxidant in one molecule. These compounds, whose parent molecule is called XJB, are the first to show recovery of mitochondrial copy number, as well as an increase in the stress response of the mitochondria.

McMurray anticipates the XJB class of compounds will move further into clinical trial, and feels they are promising therapeutics to delay the symptoms of neurodegeneration seen in Huntington's disease, even after disease progression has begun.

Environmental connections

Interestingly, Huntington's disease, a genetic disorder, is very similar in pathology to exposure-related effects of the natural herbal toxin 3-nitropropionic acid (3-NP). The mutant protein involved in HD and 3-NP both induce mitochondrial toxicity, and McMurray and colleagues have found their mechanisms and cellular pathology to be very similar.

Thus, McMurray's research to expand the potential therapeutics for HD and similar genetic conditions may also be applicable to exposures to environmental toxins such as 3-NP.

The new anatomy

In their investigation of mitochondrial dysfunction and region-specific brain toxicity in Huntington's disease, McMurray and her colleagues at LBNL found current technology inadequate. Their observation led to the utilization of the breakthrough new technology [Nanostructure-Initiator Mass Spectrometry \(NIMS\)](#).

NIMS technology enables the profiling of metabolites in specific regions of tissues, for example in brain sections, with very high resolution, opening the door for a new understanding of the cell-specific targets for exposure and disease.

The ability to look at metabolites in single cell types, through NIMS technology, has far-reaching potential for basic research and biomarker development, and may pave the path toward a better understanding of why cell type-specific toxicity occurs, as well as reveal new therapeutic possibilities.

Other suggestions included creating a listserv to extend the conversation, identifying other stakeholders in RTP and elsewhere, investigating other databases with the specific objective of discovering what ontologies they use, and meeting regularly as a group. Several attendees expressed an interest in raising visibility through publications in appropriate journals, such as *Environmental Health Perspectives*, and trade publications.



NIEHS Mitochondrial DNA Replication Group biologist [Maggie Humble](#) listened, as attendees asked questions after McMurray's lecture. (Photo courtesy of Steve McCaw)



NIEHS health scientist administrator [Dan Shaughnessy, Ph.D.](#), introduced McMurray and moderated the discussion after the lecture. (Photo courtesy of Steve McCaw)

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)

[Return to Table of Contents](#)

A plan for revolutionizing toxicology testing for the 21st century

By Heather Franco

“The difficulty lies not so much in developing new ideas as in escaping from old ones.” — John Maynard Keynes

While this quote concluded the July 17 NIEHS Office of the Director seminar by grantee [Thomas Hartung, M.D., Ph.D.](#), it expressed the overarching theme of his presentation, “The Human Toxome, Evidence-Based Toxicology, and Integrated Testing Strategies — Additions to the Toolbox of 21st Century Toxicology?” The talk was hosted by NIEHS and NTP Director Linda Birnbaum, Ph.D., who described Hartung as one of the leaders in the field of predictive toxicology.

Hartung discussed a three-pronged approach for the future of toxicology testing, utilizing organotypic cultures, pathways of toxicity (PoT), and integrated testing strategies (ITS). This 21st century toxicology toolkit seeks to revolutionize the field, opening up avenues for biomarker identification, the identification of nonhazardous chemicals, and greener design through predictive toxicology.



Hartung said the threats involved in terrorism and warfare helped to boost interest in organotypic cultures, because of the inadequacy of animal models. “It is an area which is producing a lot of excitement about making cell systems better and standardizable, so they can be used for some kind of testing.” (Photo courtesy of Steve McCaw)

Renowned pioneer in alternative testing strategies

Hartung has won several international awards for his work on alternative testing strategies. Head of the European Centre for the Validation of Alternative Methods from 2002 to 2008, he currently holds joint appointments at Johns Hopkins University (JHU) in Baltimore and the University of Konstanz in Germany. Hartung also serves as the Director for the JHU [Center for Alternatives to Animal Testing](#).

His background in pharmacology and toxicology inspired Hartung to lead the shift in toxicology testing away from animal and single-cell studies, toward a systematic approach centered on validation and pathway analyses. Through this approach, he hopes to develop a human toxome that integrates information and serves as a reference for the toxicology field.

Novel three-pronged approach for 21st century toxicology testing

Hartung's approach takes concepts from evidence-based medicine and applies them to toxicology testing. Evidence-based medicine uses a three-pronged approach to make vast amounts of data accessible to the medical community, by systematically reviewing the literature, weighing the quality of the information, and performing meta-analyses to statistically evaluate results from different studies. As part of the [Evidence-based Toxicology Collaboration](#), Hartung has adapted this approach to toxicology testing, focusing on organotypic cultures, PoT, and ITS.

As Hartung explained, the premise behind the development of organotypic cultures is that validated animal models for toxicology testing are not readily available, necessitating the development of alternative testing strategies. One strategy, the Human on a Chip, cultures multiple cell types on a chip with compartmentalized microenvironments. While there is much interest in this particular technology, Hartung cautioned that it would not solve all of the issues of toxicology testing. Thus, there is more work to be done to develop alternative testing strategies.

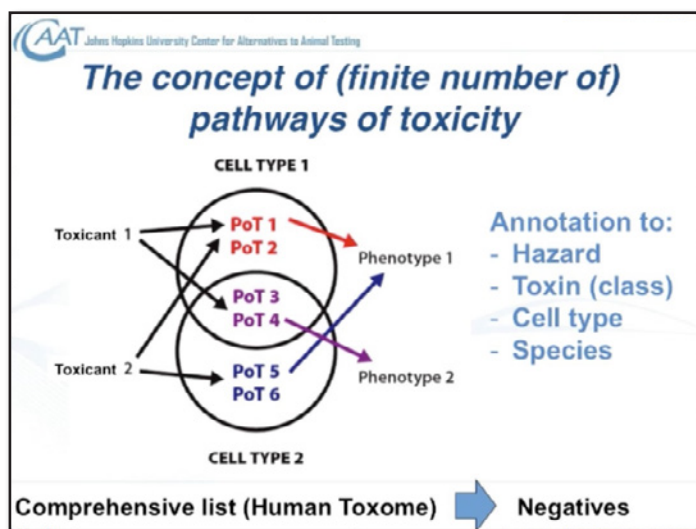
The crux of Hartung's approach is to strengthen the predictive power and validation of tests, by utilizing overlapping strategies and integrating them. "ITS are very much the baby of [REACH](#)," said Hartung, "The REACH (registration, evaluation, authorisation, and restriction of chemical substances) legislation ... requires that animal tests are only used as a last resort, but that all other information sources are used ... which requires some integration. Toxicology of the 21st century will make more and more use of ITS."

Integrated Testing Strategies

- Key contribution to REACH implementation process
- Use of different informations, not stand-alone replacement
- Interim decision points
- Probabilistic / Bayesian approaches
- Modeling and Machine Learning

Toxicology will make more use of integrated testing strategies

According to Hartung, REACH, with its prioritization of alternative test methods, has raised awareness of what ITS has to offer predictive toxicology. (Slide courtesy of Thomas Hartung)



Hartung envisions the integration of PoT for hazard identification, as well as for identifying compounds that may be useful in safe-by-design efforts. (Slide courtesy of Thomas Hartung)

The final arm of Hartung's approach, which is used in his laboratory, uses PoT to develop the human toxome (see text box). The theory behind PoT is that a particular chemical, in the same experiment, may not always affect the same genes, but will affect clusters of pathways. These pathways are analyzed to determine the hazardous or nonhazardous impact of the chemical. The resulting pathways of toxicity are then annotated and assembled to form the human toxome.

As Hartung explained, this approach to toxicology testing is like starting to drive a car while building it on the road. Although this revolution is in its early stages and much work remains to be done, Hartung said great progress has been made in the development and implementation of the toolkit, with the ultimate goal of improving human health.

Citations and Further Reading:

Hartung T. 2009. Food for thought ... on evidence-based toxicology. *ALTEX* 26(2):75-82.

Hartung T, Luechtefeld T, Maertens A, Kleensang A. 2013. Integrated testing strategies for safety assessments. *ALTEX* 30(1):3-18.

Stephens ML, Andersen M, Becker RA, Betts K, Boekelheide K, Carney E, Chapin R, Devlin D, Fitzpatrick S, Fowle JR 3rd, Harlow P, Hartung T, Hoffmann S, Holsapple M, Jacobs A, Judson R, Naidenko O, Pastoor T, Patlewicz G, Rowan A, Scherer R, Shaikh R, Simon T, Wolf D, Zurlo J. 2013. Evidence-based toxicology for the 21st century: opportunities and challenges. *ALTEX* 30(1):74-103.

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the Reproductive Developmental Biology Group of the NIEHS Laboratory of Reproductive and Developmental Toxicology.)

[Return to Table of Contents](#)



Not surprisingly, Acting Director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods Warren Casey, Ph.D., center, and other NTP scientists with interests in alternative test methods and predictive toxicology, were on hand for Hartung's talk. (Photo courtesy of Steve McCaw)

Breast cancer cell lines are being used to develop the human toxome

As part of a multi-institution NIH Transformative Research grant, Hartung uses standardized *in vitro* cell culture protocols to generate omic datasets that can be used to develop software tools for analyses to identify PoT.

In his experiments, Hartung treats MCF-7 breast cancer cells with estrogenic compounds, and determines their metabolome and transcriptome. Using newly developed software, his group, in collaboration with Agilent, has identified pathways that are impacted by the estrogenic compounds. The identified pathways are in agreement with the known roles of estrogen signaling in MCF-7 cells. Hartung said he plans on validating the system using other cell lines, such as T47D breast cancer cells, and expanding the panel of compounds used in the assay.

While these current experiments have not identified novel pathways, they have provided a means by which to develop the protocols and technologies necessary for future experiments. As Hartung explained, "These experiments are sharpening the tools for pathway identification." He hopes that these will be some of the first studies towards the development of the [human toxome](#).

LSB speaker discusses the role of RNase H2 in Aicardi- Goutieres Syndrome

By Deepa Singh

A seminar at NIEHS June 21 focused on two interesting consequences of unremoved ribonucleotides misincorporated into DNA — genomic instability and growth arrest.

[Andrew Jackson, Ph.D.](#), a clinical geneticist in the Medical Research Council Human Genetics Unit at the University of Edinburgh, provided clear evidence that misincorporated ribonucleotides are the most common endogenous base lesions in the mammalian genome, occurring at a frequency of least 1 million sites per replicating cell.

The talk, hosted by Laboratory of Structural Biology (LSB) visiting fellow Anders Clausen, Ph.D., also established that the ribonuclease H2 (RNase H2) enzyme is responsible for removing these misincorporated ribonucleotides, and that mutations in this enzyme cause Aicardi-Goutieres syndrome (AGS) in humans.

AGS is an autosomal-recessive disorder caused by mutations in the genes encoding all three subunits of a heterotrimeric RNase H2, (H2A, H2B, and H2C). According to Jackson, AGS mimics viral infection in several significant ways and has similarities to autoimmune disorders, suggesting that a better understanding of the cause and progression of AGS may also yield insights into disease processes involved in other conditions ([see text box](#)).

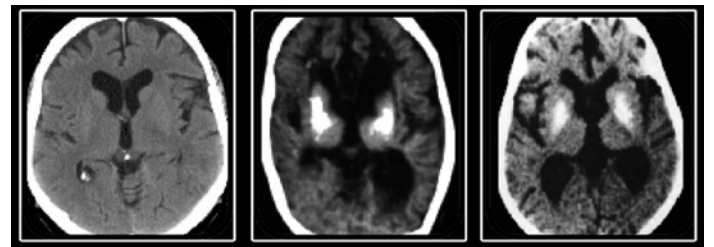
RNase H2 in mammals — growth defects and viability

During his graduate studies, Jackson focused on the genes whose dysfunction can lead to neurological disorders, and was also part of the group that mapped the two AGS gene loci AGS1 and AGS2 using homozygosity mapping. Later, Jackson's group, along with Yanick Crow, Ph.D., of the University of Manchester, were involved in the identification of three different genes, which, when mutated, can cause AGS. Research in his lab has also shown the nature of human RNase H2 protein complex, for the first time, using molecular genetics.

Through some of his protein structural work, Jackson demonstrated that AGS-causing mutations in RNase H2 were clustered around the catalytic site of the enzyme, or situated at the interface of the three subunits. Most of these latter mutations destabilized the protein, due to their reduced level of expression in the cell, and, therefore, had reduced level of enzyme function.



Clausen, left, and Jackson relaxed, following a talk that attracted a standing-room-only audience of scientists from NIEHS and area biomedical research centers. (Photo courtesy of Steve McCaw)



normal AGS congenital HIV

When he discussed these images of the brain, Jackson said he was struck by the similarities between the AGS brain and the brain of an individual infected at birth with the human immunodeficiency virus (HIV). (Image courtesy of Andrew Jackson)

To get insight into the biological role of RNase H2 *in vivo*, Jackson's group has created an RNase H2 mouse model. "The aim was to generate a neurological model, which would more accurately reflect the human condition, AGS," explained Jackson. However, a knock-in mouse model containing an A174T mutation in exon 7 of the H2B subunit, which recapitulates the most common human mutation, survived without any convincing phenotypes. But Rnaseh2bE202X/E202X mice, in which a stop codon was introduced serendipitously, was required for embryonic viability of mice, as the homozygous animals with the same alleles were not viable. These mice were also reduced in size from gastrulation, and this growth arrest was due to the activation of p53, which could be the consequence of activated DNA damage signaling, such as single or double-strand breaks in DNA.

RNase H2, a surveillance enzyme

Jackson emphasized that in mammals, RNase H2 DNA repair activity is required for the correct removal of misincorporated ribonucleotides embedded within the genomic DNA. In RNase H2 null cells, either single or di-ribonucleotides are covalently incorporated by major replicative polymerases during DNA replication. According to Jackson, "Ribonucleotides are the most common noncanonical nucleotides found in mammalian DNA." Much of this work was inspired by similar studies reported on ribonucleotide misincorporation into DNA by yeast DNA replicative polymerases, from the NIEHS LSB DNA Replication Fidelity Group, headed by [Thomas Kunkel, Ph.D.](#)

Jackson concluded his talk by describing the good (presence of RNase H2), the bad (no RNase H2), and the ugly (reduced levels of RNase H2) consequences of ribonucleotides in the genome. Ribonucleotides can act as a signal for the mismatch repair proteins, when errors are introduced during leading strand DNA synthesis, which is evident from work by [Scott Lujan, Ph.D.](#), an Intramural Research Training Award fellow in Kunkel's group. While reduced RNase H2 activity could be tolerated by the cell, potentially causing auto-inflammation as seen in AGS, lack of RNase H2 activity can cause genome instability.

(Deepa Singh, Ph.D., is a visiting fellow in the NIEHS Mechanisms of Mutation Group.)

Nucleases that mimic viral infection

AGS is a syndrome that mainly affects the brain, the immune system, and the skin. The clinical feature of AGS, a severe autoimmune disorder, mimics those of acquired *in utero* viral infection of the brain. This syndrome mostly affects newborns and infants, resulting in severe mental and physical handicaps.

Many newborns with AGS do not show any signs of the disorder at birth, but later on develop feeding problems, become irritable, develop fever, start having seizures, have abnormal posturing of limbs, and then progress to a state of profound neurological disability. During this progression, white blood cells and inflammation-associated molecules can be detected in the cerebrospinal fluid that surrounds the brain and spinal cord. These abnormal findings are consistent with inflammation and tissue damage in the central nervous system.

The symptoms, such as chilblain skin lesions on fingers, toes, and ears that manifest in 40 percent of the patients, are remindful of the autoimmune disease Systemic Lupus Erythematosus with cutaneous involvement. Most people with this disorder do not survive past childhood, but some affected individuals, with later onset and milder neurological problems, may live into adulthood. Loss of function mutations in the genes of TREX1, SAMHD1, and RNase H2 has been identified in patients with AGS.

Because AGS is a monogenic disorder with a defined molecular basis, Jackson's group is using it as a model for common autoimmune disease, to explore the cellular pathogenesis and molecular pathways implicated in nucleic acid-triggered inflammatory responses.

NIEHS fellows honored with 2014 FARE awards

By Sheila Yong

NIEHS continued its tradition of research excellence, this summer, as 19 of its fellows received the 2014 Fellows Award for Research Excellence (FARE). Although NIEHS is in the midrange in terms of size and budget among the NIH institutes and centers (ICs), it ranked in the top 26 percent in the number of fellows receiving FARE awards.

“The continued success of our trainees in receiving these awards is a testament to the high-quality training environment fostered at the Institute. The collective effort to create and sustain an outstanding environment is reflected in the persistent influx of exceptional fellows that comprise the trainee community,” said Tammy Collins, Ph.D., director of the NIEHS Office of Fellows’ Career Development.

Cash award promotes professional development

The 2014 FARE award program is sponsored by the NIH Fellows Committee, Scientific Directors, and Office of Intramural Training and Education, and is funded by the Scientific Directors. Earlier this year, fellows submitted their [research abstracts](#), which were then ranked by study sections comprised of previous FARE awardees and NIH senior scientists. Abstracts in the top 25 percent in each study section were selected, based on scientific merit, originality, experimental design, and overall quality and presentation.

Winners of the FARE awards will each receive a \$1,000 stipend to attend a scientific meeting of their choice, at which they will present their research. They are also invited to present a poster at the annual NIH Research Festival and attend the FARE awards ceremony held on the NIH Bethesda, Md., campus in October, as well as to judge the following year’s FARE competition. Furthermore, the recipients will be recognized at the NIEHS Director’s Awards ceremony.

2014 awards set new records

Of the 19 awardees, six came from the Laboratory of Toxicology and Pharmacology (LTP), setting a new record for a single laboratory or branch at NIEHS. The LTP winners are Christopher Campos, Ph.D.; Neal Englert, Ph.D.; Ngome Makia, Ph.D.; Stela Palii, Ph.D.; Lindsay Smith, Ph.D.; and Qingshan Wang, M.D.

Winning on their first try

Of the first-time winners, several were also first-time applicants. Among them is Mahita Kadmiel, Ph.D., from LST, who had been at NIEHS for only a year at the time of her application. Though she did not feel that her abstract was competitive enough for a FARE award, she was grateful to her mentor, Cidlowski, who made sure all the trainees in his group applied for the award. “The fact that the abstracts get peer-reviewed in a blind study section makes this award more valuable to me,” she noted.

Jeremy Weaver, Ph.D., another first-time applicant and awardee from LST, said that he and his mentor, Stephen Shears, Ph.D., went through seven drafts before submitting the final version of his abstract. “We tried to incorporate an introduction, the experimental procedures, our findings, and the significance of the research, while still obeying the character limit. It was challenging, but well worth the effort, because it helped me summarize my thoughts and ideas,” he said.

First-time winner Erica Ungewitter, Ph.D., mentored by Humphrey Yao, Ph.D., of the Laboratory of Reproductive and Developmental Toxicology, had this to offer future FARE award applicants. “It appears that the section that you choose for judging can have a big impact on your chances of winning,” she observed, adding that she and her labmates tried to select different sections to avoid competing against one another. This piece of advice may motivate future applicants to put more thought into preparing their abstracts and categorizing their research.

Smith was the most impressive, having won the award for the third time. “It is wonderful to be recognized for all my hard work, especially by such a diverse judging panel,” she commented. Now an Intramural Research Training Award (IRTA) fellow mentored by David Miller, Ph.D., Smith won her first FARE award as a predoctoral fellow, mentored by John Cidlowski, Ph.D., from the Laboratory of Signal Transduction (LST).

Five other FARE awardees were second-time winners:

- Wang, from the Laboratory of Toxicology and Pharmacology, mentored by Jau-Shyong (John) Hong, Ph.D.
- Huaixin Dang, Ph.D., Kristin Lichti-Kaiser, Ph.D., and Gary ZeRuth, Ph.D., from the Laboratory of Respiratory Biology, mentored by Anton Jetton, Ph.D.
- Bonnie Joubert, Ph.D., from the Epidemiology Branch, mentored by Stephanie London, M.D., Dr.P.H.

Many awardees agreed that competing for the FARE award inspired them to critically evaluate the importance of their research, and how they can present their findings more effectively to a diverse audience.

“The FARE award allows young researchers to evaluate how their work will be received by other scientists, some of whom may work in different disciplines,” Joubert noted. She thinks that winning the award gives fellows the confidence and encouragement to publish and present their research, and motivates them to further pursue their ideas.

“Attendance at national scientific meetings is an integral part of learning to be an interactive scientist,” said NIEHS Deputy Scientific Director Bill Schrader, Ph.D. “In this time of tightened travel budgets, the FARE awards program is the best way for trainees to increase their participation at meetings in their specialty fields.”



IRTA fellow Christopher Campos, Ph.D., “Transient barrier disruption increases transport function at the blood-brain barrier,” mentor David Miller, Ph.D. (Photo courtesy of Steve McCaw)



Visiting fellow Senthilkumar Cinghu, Ph.D., “Meta-analysis identifies key determinants of embryonic stem cell identity and homeostasis,” mentor Raja Jothi, Ph.D. (Photo courtesy of Steve McCaw)



Visiting fellow Huaixin Dang, Ph.D., “TAK1/TR4 regulates cold induced thermogenesis by inhibiting CREB-PGC1 α pathway,” mentor Anton Jetten, Ph.D. (Photo courtesy of Steve McCaw)



IRTA fellow Neal Englert, Ph.D., “Epigenetic Modification of Histone (H3) and CYP2C9 Regulation: Involvement of Med25 as the Key Regulator,” mentor Joyce Goldstein, Ph.D. (Photo courtesy of Steve McCaw)



IRTA fellow Bret Freudenthal, Ph.D., “The Polymerase Reaction Exposed: Observing a DNA Polymerase Choose Right from Wrong,” mentor Samuel Wilson, M.D. (Photo courtesy of Steve McCaw)



IRTA fellow George Fromm, Ph.D., “Pausing of RNA Polymerase II Regulates Mammalian Developmental Potential,” mentor Karen Adelman, Ph.D. (Photo courtesy of Steve McCaw)



Research fellow Bonnie Joubert, Ph.D., “Maternal smoking and DNA methylation in newborns: An in utero effect or epigenetic inheritance?” mentor Stephanie London, M.D., Dr.P.H. (Photo courtesy of Steve McCaw)



Visiting fellow Mahita Kadmiel, Ph.D., “Glucocorticoid receptor action at the interface with the environment,” mentor John Cidlowski, Ph.D. (Photo courtesy of Steve McCaw)



IRTA fellow Nevzat Kazgan, Ph.D., “Intestine-specific deletion of SIRT1 alters systemic lipid and bile acid homeostasis in mice,” mentor Xiaoling Li, Ph.D. (Photo courtesy of Steve McCaw)



*IRTA fellow YuanYuan Li, Ph.D.,
“T-KDE: A method for analyzing
genome-wide protein binding patterns
from ChIP-seq data,” mentor Leping Li,
Ph.D. (Photo courtesy of Steve McCaw)*



*IRTA fellow Kristin Lichti-Kaiser, Ph.D.,
“Transcription Factor Glis3 Plays a
Critical Role in the Development of
Functional Pancreatic beta-cells and
Diabetes,” mentor Anton Jetten, Ph.D.
(Photo courtesy of Steve McCaw)*



*Visiting fellow Ngome Makia, Ph.D.,
“Activator Protein 1 Regulation of Human
CYP2C9 Expression by Electrophilic
Stress Involves MAPK Activation and
DNA Looping,” mentor Joyce Goldstein,
Ph.D. (Photo courtesy of Steve McCaw)*



*IRTA fellow Stela Palii, Ph.D.,
“Combined disruption of ATM and CHK1
functionalities reveals redundancies in
the DNA damage response pathways
and results in synthetic growth inhibition
following gamma-irradiation,” mentor
Richard Paules, Ph.D. (Photo courtesy of
Steve McCaw)*



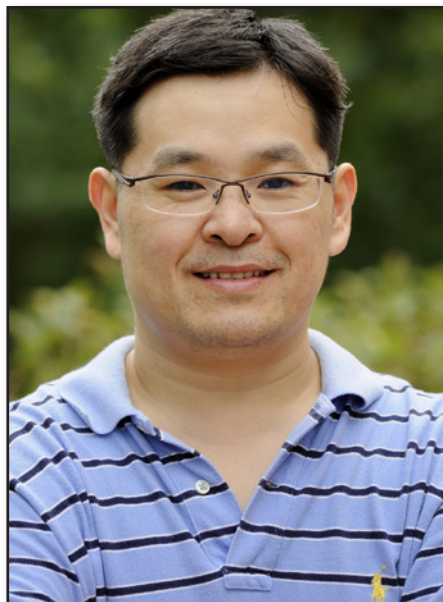
*IRTA fellow Sabrina Robertson, Ph.D.,
“Developmental origins of central
norepinephrine neuron diversity,”
mentor Patricia Jensen, Ph.D. (Photo
courtesy of Steve McCaw)*



*IRTA fellow Lindsay Smith, Ph.D.,
“Glucocorticoid Receptor Regulation of
P-glycoprotein at the Blood-Brain and
Blood-Spinal Cord Barriers,” mentor
David Miller, Ph.D. (Photo courtesy of
Steve McCaw)*



*IRTA fellow Erica Ungewitter, Ph.D.,
“GLI-similar 3 Maintains Sexually
Dimorphic Germ Cell Development in
Mouse Embryos,” mentor Humphrey Yao,
Ph.D. (Photo courtesy of Steve McCaw)*



*Visiting fellow Qingshan Wang, M.D.,
“Endogenous substance P regulates
microglial density in substantia nigra
through neurokinin-1 receptor/NADPH
oxidase axis-mediated chemotaxis,”
mentor Jau-Shyong (John) Hong, Ph.D.
(Photo courtesy of Steve McCaw)*



*IRTA fellow Jeremy Weaver, Ph.D.,
“Kinetic evaluation of an inositol
pyrophosphate kinase reveals its signaling
credentials,” mentor Stephen Shears,
Ph.D. (Photo courtesy of Steve McCaw)*



*Research fellow Gary ZeRuth, Ph.D.,
“The Krüppel-like protein Gli-similar 3
(Glis3) functions as a key regulator of
insulin transcription,” mentor Anton Jetton,
Ph.D. (Photo courtesy of Steve McCaw)*

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

[Return to Table of Contents](#)

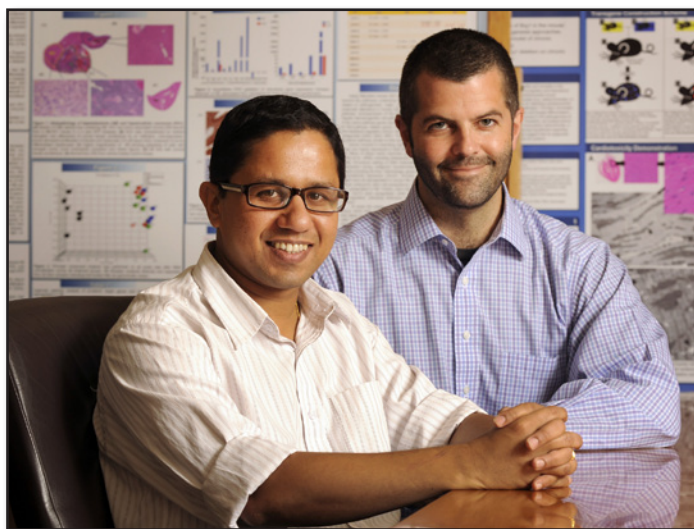
NTP postdocs recognized with Society for Toxicologic Pathology awards

By Eddy Ball

NTP postdocs won two of the three Young Investigator Awards presented at this year's Society of Toxicologic Pathology (STP) [annual meeting](#) June 16-20 in Portland, Ore.

The NTP awardees are Sachin Bhusari, D.V.M., Ph.D., who placed first, and Michael Boyle, D.V.M., who placed third. Bhusari is a member of the Cellular and Molecular Pathology Branch (CMPB) Investigative Pathology Group, headed by pathologist [Mark Hoenerhoff, D.V.M., Ph.D.](#)

Boyle is part of the CMPB NTP Pathology Group, headed by pathologist [David Malarkey, D.V.M., Ph.D.](#), and is also being mentored in his Ph.D. research, on the modulation of chromatin-remodeling factors in cardiovascular development and disease, by NIEHS lead researcher Trevor Archer, Ph.D., head of the Laboratory of Molecular Carcinogenesis.



Bhusari, left, and Boyle were recognized by the world's leading professional organization in the advancement of pathology, as it pertains to changes elicited by pharmacological, chemical, or environmental agents, as well as factors that modify these responses. STP membership includes some 1,250 scientists and professionals in more than 28 countries. (Photo courtesy of Steve McCaw)

Kudos for the winners and for NTP

Both awardees earned high praise on the quality of their research and the impact that this research has on the scientific community ([see text box](#)) from their mentors, as well as from CMPB head Robert Sills, D.V.M., Ph.D. In addition to acknowledging the superior work by the trainees, Hoenerhoff said, "This award also reflects highly on the high standards of quality the NTP has achieved in terms of training and research."

"Ours is the only program of its kind in the U.S. and the world. Trainees learn rodent pathology, provide institute support, work on NTP projects, and prepare for board certification by the American College of Veterinary Pathologists (ACVP)," added Malarkey, who has been instrumental in establishing a formalized and successful NIEHS Toxicological Pathology Training Program. "There have been 13 pathology trainees in the program since 2003, with 11 becoming board-certified by the American College of Veterinary Pathologists (ACVP), and 4 simultaneously pursuing, or having received, a Ph.D. from NCSU [North Carolina State University]."

Well-deserved recognition

"Receiving first place in the Society of Toxicologic Pathology Young Investigator Awards is a very significant accomplishment for Dr. Bhusari," Hoenerhoff explained. "This award is one of many that he has been awarded during his time at NTP, and is really a testament to his dedication to toxicology and cancer research." Among Bhusari's earlier accomplishments was earning recognition as a Diplomate of the American Board of Toxicology (ABT), one of the profession's top certifications.

According to Malarkey, in addition to his work on NTP studies, Boyle also assists NIEHS intramural researchers in the design, implementation, and evaluation of animal studies. He is an ACVP board-certified veterinary pathologist, and currently pursuing certification by ABT, in addition to his Ph.D. research.

Award-winning research

- **Bhusari S**, Pandiri A, Wang Y, Foley J, Hong H-H, Ton TVT, Shockley K, Peddada S, Gerrish K, Malarkey D, Sills R, Hoenerhoff M. 2013. Transcriptomic Profiling of Hepatoblastomas and Associated Hepatocellular Carcinomas in B6C3F1 Mice. Unpublished meeting abstract.

A team of NTP and NIEHS researchers identified global transcriptomic changes in chemically induced hepatoblastomas (HB), associated hepatocellular carcinomas (HCC), tumor adjacent normal liver, and vehicle control liver to define gene expression patterns informative of the pathogenesis of HB in mice and its human relevance. Using frozen samples from a 2-year NTP bioassay in B6C3F1 mice that were laser capture microdissected, the team of scientists performed microarray analysis to identify differentially expressed genes between sample groups.

Transcriptomic analysis using Ingenuity Pathway Analysis revealed significant alterations in hepatic development and embryonic stem cell regulation, and genomic imprinting in HB compared to HCC. These genomic alterations were also relevant to the pathogenesis of human HB, and the findings point to a potential for more accurate assessment of chemically induced hepatocarcinogenesis and its human relevance in hazard identification.

- **Boyle MC**, Hoffman JA, Malarkey DE, Archer TK. 2013. Deletion of the Chromatin-Remodeling Factor Brg1 Confers Sensitivity to Doxorubicin Cardiotoxicity in Mice. Unpublished meeting abstract.

NTP Pathologists Boyle and Malarkey and NIEHS cancer biologists Hoffman and Archer conducted experiments involving chronic exposure of wild-type and Brg1 transgenic knockout (KO) mice to doxorubicin, a cancer chemotherapeutic known to produce cardiotoxicity, a primary or comorbid factor involved in cardiovascular disease. The engineered mice were the outcome of an inducible deletion of the chromatin-remodeling factor Brg1.

The researchers found lesions consistent with chronic anthracycline cardiotoxicity in all treated mice, including multifocal discrete sarcoplasmic vacuolar degeneration and multifocal sarcoplasmic fragmentation, but were increased in Brg1 KO mice. They concluded the increased number and severity of lesions observed in the Brg1 KO mice suggest genetic deletion of functional units of the chromatin-remodeling factor Brg1 confers sensitivity to cardiotoxicants. In addition, they postulated that the Brg1 KO mouse is a sensitive model of cardiotoxicity for risk assessment and hazard identification.

[Return to Table of Contents](#)

NIEHS and NTP join colleagues at Teratology Society meeting

By Robin Mackar

The [Teratology Society](#) is a scientific group with a mission focused on preventing birth defects, including identification of environmental factors that affect maternal health and pregnancy outcomes. The important role this society plays in environmental health was very evident by the number of cutting-edge talks that NIEHS and NTP staff gave at its 53rd [annual meeting](#) June 22-26 in Tucson, Ariz.

Cutting-edge technologies

The theme of the annual meeting was Application of Cutting-Edge Technologies to Improve Assessment, Treatment, Prevention, and Communication Regarding Birth Defects. A special plenary lecture on "New experimental approaches for exploring the genetic/epigenetic landscape of environmental exposures" was presented by NIEHS Deputy Director Rick Woychik, Ph.D. He was introduced by Teratology Society President Edward Carney, Ph.D., director of Predictive Toxicology at Dow Chemical Company. Woychik talked about efforts in his own laboratory to use diverse stem cell populations to understand the molecular mechanisms of toxicity.



Shelby, at podium, and Howdeshell, far right, of NTP, organized a panel of experts to discuss chemotherapeutic use and pregnancy outcomes. Howdeshell also made a presentation to the NTP Board of Scientific Counselors about the new NTP monograph that same week. (Photo courtesy of Gloria Jahnke)

Cancer and pregnancy symposium

Stemming from their work on the [NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy](#), Kembra Howdeshell, Ph.D., and Mike Shelby, Ph.D., of NTP's [Office of Health Assessment and Translation \(OHAT\)](#), organized and co-chaired a symposium on Cancer and Pregnancy: Considerations Regarding the Use of Chemotherapy. Howdeshell provided an overview of the finalized monograph, which was designed as a resource document for the pregnant patient with cancer and her medical team, as they consider treatment options. More than 100 people attended the session, which was co-sponsored by the [Organization of Teratology Information Specialists](#). The symposium also received funding from NIEHS.

"We are so pleased that we could accommodate this important symposium into our scientific program" said Carney. "NTP did its usual excellent homework and pulled together an impressive panel of speakers." Carney is familiar with NTP products, as he has served as an expert panel member for evaluations of the Center for the Evaluation of Risks to Human Reproduction (now OHAT) and as a member of the NTP Board of Scientific Counselors.

During the afternoon symposium, in addition to Howdeshell's presentation summarizing the NTP monograph, speakers included cancer and fertility specialists:

- Elyce Cardonick, M.D., an obstetrician at Cooper Health System, who focused on prenatal care for the pregnant cancer patient and the need for registries to document pregnancy outcomes.
- Jennifer Litton, M.D., an oncologist at the University of Texas MD Anderson Cancer Center, spoke about some of the latest methods used for detection and administration of systemic therapies for breast cancer during pregnancy.
- Laxmi Kondapalli, M.D., a reproductive endocrinologist and fertility expert at the University of Colorado Anschutz Medical Campus, updated attendees about the field of oncofertility, or the latest methods in fertility preservation in patients with cancer.

"The information the speakers provided will be of great value to any female cancer patient and her physicians, regarding decision-making for a current pregnancy or preservation of fertility for future pregnancies," Carney added. Howdeshell said she received some excellent ideas from the panelists and the participants about next steps for disseminating the new monograph.

Diabetes and pregnancy

Gloria Jahnke, D.V.M., of the NTP Office of the Report on Carcinogens, took the lead in heading another session. Chair of the Teratology Society's Public Affairs Committee for the past three years, Jahnke co-chaired a symposium on diabetes and pregnancy with Asher Ornoy, M.D., from the Israeli Teratology Information Service. The symposium was endorsed by the Society for Maternal-Fetal Medicine, and included a stellar panel that focused on addressing how to prevent or treat the increasing number of women with diabetes that become pregnant.

"One of the things I love about the Teratology Society meetings is the diverse group of disciplines represented by those who attend the meetings and make up its membership. It makes every symposium more interesting," Jahnke said.

Other NIEHS staff participating in the meeting included Suzanne Fenton, Ph.D., and Jason Stanko, Ph.D., from the NTP Laboratory [Reproductive and Endocrinology Group](#), and [Thad Schug, Ph.D.](#), from the Extramural Research and Training Division.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)

[Return to Table of Contents](#)

Indian scholar offers global perspective on fiber nanotoxicology

By Aleksandra Adomas

Qamar Rahman, Ph.D., dean of Research Science and Technology at Amity University in India, visited NIEHS July 19 to deliver an eye-opening talk on nanotoxicology, exploring the question, "Are carbon nanotubes really following the footprints of asbestos fibers?" Hosted by NIEHS and NTP Director Linda Birnbaum, Ph.D., Rahman's presentation outlined her concerns about the public health impact of the dramatic growth in the production and use of carbon nanofibers in a wide range of consumer products, as well as the absence of effective regulatory oversight.

As the title of her talk suggests, Rahman and other researchers are increasingly worried that the morphological and adsorptive characteristics of carbon nanofibers, which are strikingly similar to asbestos, may mean they could pose a similar threat to human health. Even though the adverse effects of asbestos exposure are known, the mineral is still widely used in India, where regulation is minimal and the incidence of asbestos-related disease is on the rise.

Rahman is a strong advocate for the development of a systematic approach to nanotoxicology, and has made it her aim to unify physical, biological, and toxicological approaches with computational modeling, to better understand the impact of nanoparticles on human health.



For almost 40 years, Rahman has been actively engaged in chemical and biological research on the health effects of occupational and environmental exposure to asbestos and asbestos-like fibers. In September 2009, she became the first Indian scientist ever awarded an honorary doctorate from University of Rostock in Germany. (Photo courtesy of John Maruca)

Fiber toxicology

Carbon nanotubes (CNTs) are nanoscale cylinders made from rolled layers of graphene. Due to their exceptional mechanical, electrical, chemical, thermal, and optical properties, CNTs are used in a variety of applications. These range from structural mechanics, electronics, and clothing, to medical uses, such as the creation of artificial muscles and scaffolding for improved healing of broken bones, even in the spine. However, as Rahman pointed out, despite its benefit in terms of new and improved products, the new technology might pose a risk to human health.

According to Rahman, because CNTs are thin, long, and biopersistent, they might behave like asbestos fibers. Asbestos becomes a health concern when fibers are inhaled over a long time, leading to asbestosis, a progressive lung fibrosis, or malignant mesothelioma, a rare form of cancer, which normally takes decades to fully develop. Rahman said she is alarmed by the way asbestos exposure can act synergistically with other exposures, such as indoor air pollution, to trigger disease much more quickly.

“In unorganized sectors [in India], women using unprocessed cooking fuel develop asbestosis within five years,” Rahman said. She explained that this accelerated disease progression seems to be due to the ability of asbestos to adsorb other harmful chemicals and facilitate their delivery deep into the respiratory system.

Technology comes first

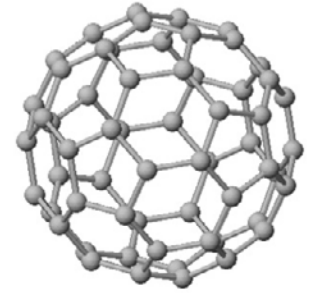
Not much is known about the potentially adverse effects of occupational exposure to CNTs.

“There are no effects reported in exposed workers [so far],” Rahman said. Animal studies have found pulmonary effects, inflammatory response, oxidative stress, and granuloma development among potential consequences of CNT exposure. But Rahman emphasized that it is not clear if fiber uptake is necessary, or if interaction with cell surface is sufficient.

Long CNT fibers have been shown to cause an asbestos-like inflammatory reaction in the pleural cavity of exposed animals, while other studies of animals exposed to short CNT fibers have found no carcinogenic response to exposure. Rahman said both carbon and asbestos fibers can lead to DNA damage, cytotoxicity, and inflammation, and they appear to regulate expression of similar genes.

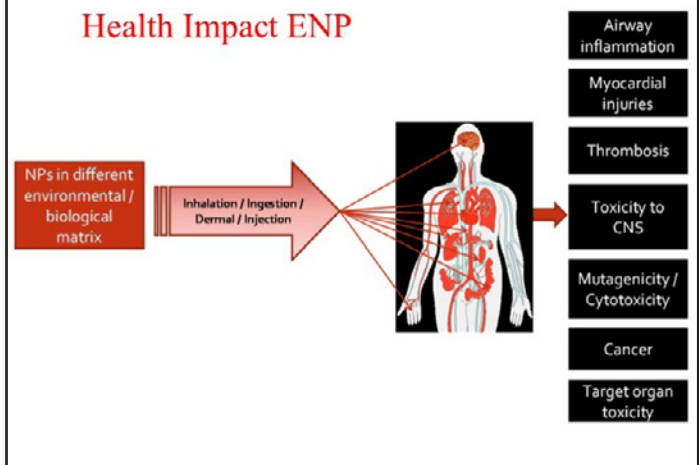
Special features of engineered nanomaterials:

- ◆ Small, reactive, surprising
- ◆ Enabling
- ◆ Different
- ◆ Huge technological and financial potential
- ◆ Risks unknown or poorly known
- ◆ 1-100 nm



CNTs differ in length, shape, dimension, physical characteristics, surface modifications, purity, and formation of agglomerates and aggregates. Single-walled CNTs consist of a single rolled graphene sheet and have a typical diameter of approximately 1-5 nanometers, while the length may be up to tens of micrometers. Multiwalled CNTs consist of many single-walled tubes, stacked one inside the other, with diameters in the range of 5-100 nanometers and length reaching several micrometers. They all offer huge technological potential because of their exceptional strength, but carry a poorly understood risk to human health. (Photo courtesy of Qamar Rahman)

Health Impact ENP



As Rahman explained, engineered nanoparticles can enter the human body through different entry points — skin, blood, respiratory, and digestive track pathways — and may result in a range of adverse biological effects. (Photo courtesy of Qamar Rahman)

Nanotoxicology development is hampered by an absence of well-defined modes of action. Proposed possible mechanisms include chromosome tangling through DNA damage, oxidative stress activating signaling cascades, chronic inflammation, and adsorption of other carcinogens on CNT fibers, but nanomaterials are difficult to characterize due to differences in manufacturing and composition. “No [two] nanoparticles are the same,” Rahman explained. “They have different dimensions and can be chemically modified in different ways.”

Because of limited data and lack of biomarkers for CNT exposure, it is difficult to reach regulatory decisions. For example, there are no safety programs in India, even though nanomaterials are used and produced. As Rahman described the regulatory situation there, “Technology is first — toxicology comes later.”



Birnbaum, right, joined Rahman during the question and answer session. Like her host, Rahman is concerned about the introduction of untested chemicals and materials that might trigger diseases, such as asbestosis, that take years or even decades to manifest. (Photo courtesy of John Maruca)

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

[Return to Table of Contents](#)

NIEHS scientists find proteins involved in immunity potentially cause cancer

By Robin Arnette

A set of proteins involved in the body’s natural defenses produces a large number of mutations in human DNA, according to a new [study](#) led by researchers at NIEHS. The findings suggest that these naturally produced mutations are just as powerful as known cancer-causing agents in producing tumors.

The proteins are part of a group called apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) cytidine deaminases. The investigators found that APOBEC mutations can outnumber all other mutations in some cancers, accounting for over two-thirds in some bladder, cervical, breast, head and neck, and lung tumors.

The scientists published their findings online July 14 in the journal *Nature Genetics*. [Dmitry Gordenin, Ph.D.](#), is corresponding author of the paper and a senior associate scientist at NIEHS. He said researchers knew the main functions of APOBEC cytosine deaminases were to inactivate viruses that attack the body, and prevent ancient viruses present in the human genome from moving around and causing disrupting mutations. Because they are so important to normal physiology, he and his collaborators were surprised to find a dark side to them — that of mutating human chromosomal DNA.

Linking mutations across the genome to the environment

The study is a follow-up to one Gordenin and his group [published](#) in *Molecular Cell* in 2012, after they discovered APOBECs could generate clusters of mutations in some cancers.

“The presence of APOBEC clusters in the genome of tumor cells indicates that APOBEC enzymes could also have caused many mutations across the genome,” Gordenin said.

Gordenin’s NIEHS team, comprised of scientists from the Chromosome Stability Group, headed by Michael Resnick, Ph.D., and the Integrative Bioinformatics Group, headed by David Fargo, Ph.D., took the 2012 research one step further, by applying a modern data science approach.

The group collaborated with co-corresponding author Gad Getz, Ph.D., and other colleagues from the Broad Institute of MIT and Harvard in Cambridge, Mass. They looked for signs of genome-wide APOBEC mutagenesis in cancers listed in The Cancer Genome Atlas, a cancer database funded and managed by the National Cancer Institute and the National Human Genome Research Institute, both part of the National Institutes of Health.

Using APOBEC’s distinctive DNA mutational signature, they examined approximately 1 million mutations in 2,680 cancer samples, and found that, in some tumors, nearly 70 percent of mutations in a given specimen resulted from APOBEC mutagenesis. The mutation pattern, which appeared in clusters and individual mutations, could affect many cancer-associated genes.

Steven Roberts, Ph.D., a postdoctoral fellow who works with Gordenin, is first author on both studies. He explained that since APOBECs are regulated by the immune system, which is responsive to many environmental factors, he believes there may be a significant environmental component to APOBEC mutagenesis.

“We hope that determining the environmental link to these mutations will lead to viable cancer prevention strategies,” Roberts said.

In upcoming work, he and Gordenin plan to address why APOBEC mutagenesis appears in some cancer types and not others.

Citation: Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA. 2013. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. Nat Genet; doi:10.1038/ng.2702 [Online 14 July 2013].

[Return to Table of Contents](#)



Gordenin, left, and Roberts said the environmental aspect of APOBEC mutagenesis is directly related the Institute’s mission, and an area they are currently investigating. (Photo courtesy of Steve McCaw)

Linked audio

[Listen to Roberts describe the duality of APOBEC \(00:29\)](#)

[Read Transcript](#)

(Launches in new window)

Download Media Player: Quicktime

Linked audio

[Listen as Gordenin discusses the advances made possible through data science \(00:46\)](#)

[Read Transcript](#)

(Launches in new window)

Download Media Player: Quicktime

Watching a polymerase be unfaithful in real time

By Robin Arnette

To make illustrations appear to come to life, animators project a sequence of drawings at high speed to create the illusion of movement. At any time, the artists may slow the process down or even stop the action to study an individual frame in detail.

In much the same way, scientists may now take snapshots of an enzymatic reaction in real time, then compile the images to view the key steps during the reaction. Others have utilized this new technique called time-resolved crystallography, but NIEHS postdoctoral fellow Bret Freudenthal, Ph.D., and colleagues William Beard, Ph.D., and David Shock, Ph.D., were the first to use the method to examine how a model human DNA polymerase beta (pol beta) chooses a nucleotide during DNA synthesis.

All three scientists are members of the NIEHS DNA Repair and Nucleic Acid Enzymology Group led by [Samuel Wilson, M.D.](#) They said since pol beta fills gaps in DNA following the excision of mutagenic damaged nucleotides, the work will help researchers better understand DNA repair and the processes that protect genomic DNA from mutations that could lead to cancer and other diseases. Their [results](#) appeared online July 3 in the journal *Cell*.

Uncovering pol beta's secrets

Wilson said the new X-ray crystallography technique confirmed features of the computational results his team and collaborators generated earlier, but revealed important surprises. They found that pol beta changes its shape depending on whether it incorporates a complementary base pair or correct nucleotide, which happens during faithful replication, or a noncomplementary base pair or incorrect nucleotide, which results in a mistake, or mutation.

The study also found that pol beta forms a third metal ion-binding site during the reaction, and likes to hang on to its reaction product pyrophosphate. Prior to this report, and other recent work, scientists believed that all polymerases used only two metal ion binding sites in their mechanism of action and released pyrophosphate instantly.

Using the new technique, Freudenthal and other colleagues performed the polymerase reaction in the crystal using pol beta and natural substrates, and froze the reaction at various time points for time-resolved crystallography. These quick peeks, in essence, slowed down the reaction about 100-fold, and allowed them to observe pol beta making critical decisions in molecular detail.

“Typically, with an enzyme like this, you’d have to look really fast because the entire reaction would be over in one second,” Wilson said. “This method allows you to observe the reaction in whole seconds, rather than a nanosecond timescale.”



Freudenthal, who won a 2014 NIH Fellows Award for Research Excellence for work leading to this study, is first author on the paper. “By utilizing the technique, we were able to look at steps that have effects on the downstream signals following DNA repair,” he said. “We can now get a feel for how things are handled in the cell.” (Photo courtesy of Steve McCaw)

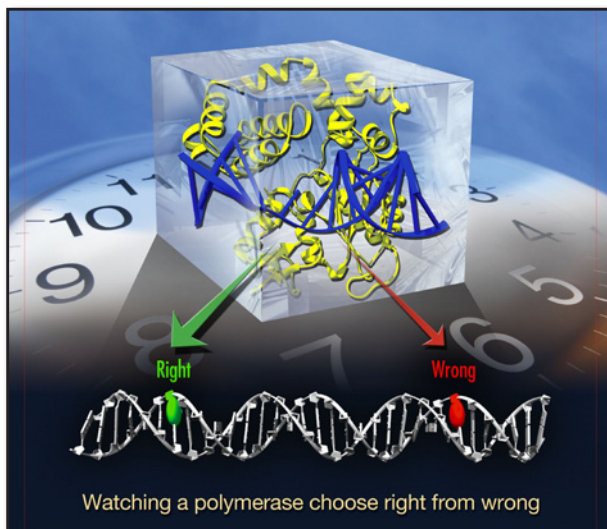
Differences between right and wrong

Freudenthal found that if pol beta incorporated the wrong nucleotide, the polymerase switched to an open configuration, which released the two products normally generated by the reaction, newly synthesized DNA and pyrophosphate. If it incorporated the right nucleotide, the pyrophosphate remained for an extended time and prevented pol beta from changing to the open structure and releasing pyrophosphate. This pyrophosphate hang-up or delay following correct incorporation could facilitate downstream channeling of DNA substrates during DNA repair. In contrast, the rapid release following incorrect incorporation may facilitate passage to alternative DNA repair pathways or release of pol beta from DNA.

Freudenthal explained it this way. “Time-resolved crystallography revealed that the speed of the reaction and the shape of pol beta vary if the incorrect base pair is used. Are these differences important to figuring out how abnormal DNA repair leads to cancer? Right now, we don’t know, but we’re a bit closer to teasing out the processes that may be crucial.”

Although the technique used in this work is called time-resolved crystallography, Freudenthal also likes to call it time-lapse crystallography because the procedure reminds him of the time-lapse photography used in some animated features. Regardless of the name, he’s sure other researchers will use the approach to make their own enzymatic movies and, in the process, learn more about the potential causes of disease.

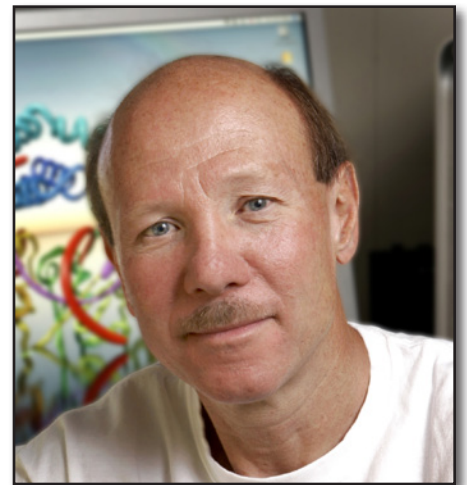
Citation: [Freudenthal BD, Beard WA, Shock DD, Wilson SA. 2013. Observing a DNA polymerase choose right from wrong. Cell 154\(3\): 157-168.](#)



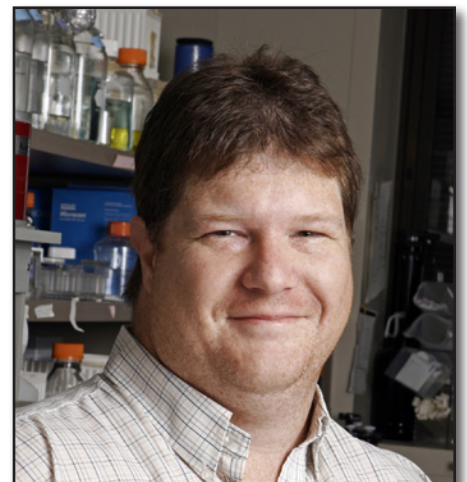
DNA polymerases must choose a nucleotide from a pool of structurally similar molecules to preserve Watson-Crick base pairing during DNA replication and repair. This diagram illustrates a crystallized DNA polymerase making a temporal decision to incorporate a right or wrong nucleotide. (Design by Bret Freudenthal and artwork by Donna Corcoran)



“In general, the results are consistent with previous observations, but we had not actually seen the incorrect incorporation occur until now,” Wilson said. (Photo courtesy of Steve McCaw)



As a staff scientist in Wilson’s group, Beard has participated in several breakthroughs involving DNA repair. (Photo courtesy of Steve McCaw)



Shock used his expertise as a research chemist to contribute to the work. (Photo courtesy of Steve McCaw)

Using gene expression data to map the mouse brain

By Robin Arnette

If you're planning a fun-filled weekend of hiking and camping, bringing along a map of the area is a good idea. What would happen, though, if that map included mountains and lakes of the terrain, but lacked roads, bridges, and footpaths? Finding your way around the landscape wouldn't be impossible. Yet, knowing how everything connected would make the adventure more enjoyable.

Scientists in the NIEHS Developmental Neurobiology Group, led by [Patricia Jensen, Ph.D.](#), had a similar problem, when they began studying a set of neurons in the brainstem of adult mice. These neurons make and release norepinephrine (NE), a molecule that acts as a hormone and neurotransmitter. Jensen knew, in general, their form and structure, and where NE neurons were positioned, but nothing about their cellular organization or the neural highways they used to communicate with different regions of the brain.

Jensen's work appeared [online](#) July 14 in *Nature Neuroscience*, and revealed, for the first time, a roadmap of NE neurons in the rodent brain. Since these nerve cells are involved in a wide range of behaviors and physiological processes, such as maintaining attention, sleep, food intake, and memory, the research has important implications for conditions as varied as Parkinson's disease and mental health disorders.

Tracking NE neurons and their connections

Prior to this work, neuroscientists categorized NE neurons into six separate nuclei, or groups based on their anatomical structure, in the adult mouse brain. But, Jensen's team developed a novel way to classify NE neurons based on the gene expression differences they exhibit during early mouse development.

Jensen explained that the hindbrain of a fetal mouse, like that of a human fetus, is divided into 8 segments called rhombomeres, each of which expresses a unique combination of genes. Adult NE neurons that are derived from a particular rhombomere will have the same gene expression pattern ([see illustration](#)). With this information, Jensen now has the ability to manipulate various classes of NE neurons in mice and study the behavioral consequences.



Jensen is the newest member of the NIEHS Laboratory of Neurobiology, joining the Institute in 2009. (Photo courtesy of Steve McCaw)



Robertson is a postdoctoral fellow in Jensen's group, and was one of 19 NIEHS trainees who received a 2014 NIH Fellows Award for Research Excellence (FARE). The award provides recipients with funds to travel to a scientific meeting of their choice. (Photo courtesy of Steve McCaw)

“Dividing NE neurons according to gene expression differences shows how diverse this small population of neurons is,” Jensen said. “We hope to gain insight into why certain populations of NE neurons may be vulnerable to environmental insult or disease.”

Two members of Jensen’s lab, Sabrina Robertson, Ph.D., and Nicholas Plummer, Ph.D., shared first authorship of the paper, and said the article shattered another long-held belief in the field. Neuroscientists presumed that all of the NE released in the cortex — the outer furrowed portion of the brain important in higher-order thinking — came from one cluster of NE neurons in the locus coeruleus (LC), a small section of the brainstem that processes the body’s sensory signals. They found that other NE neurons, outside of the LC region, communicate with the cortex as well.

“We observed that certain subpopulations of NE neurons were talking to different regions of the brain, which suggested the gene expression pattern of a nascent NE neuron may contribute to the function of that NE neuron in the adult,” Robertson said.

NE neurons implicated in human disease

Researchers have implicated NE neuron dysfunction in a number of mental health disorders, and have determined that NE neurons are lost in Parkinson’s disease, Alzheimer’s disease, and Down syndrome, also known as trisomy 21. These neurons are also disrupted following exposure to toxicants, such as 1-bromopropane or ozone.

Because of the influence NE neurons have on the brain, pharmaceutical companies have manufactured products that focus on their activity. Several medications on the market today, such as antidepressants and prescriptions for attention deficit hyperactivity disorder, target NE neurons.

With this new NE neuron roadmap, Jensen and other neuroscientists will be able to navigate through the brain, on a journey to better treatments for neurological disorders.

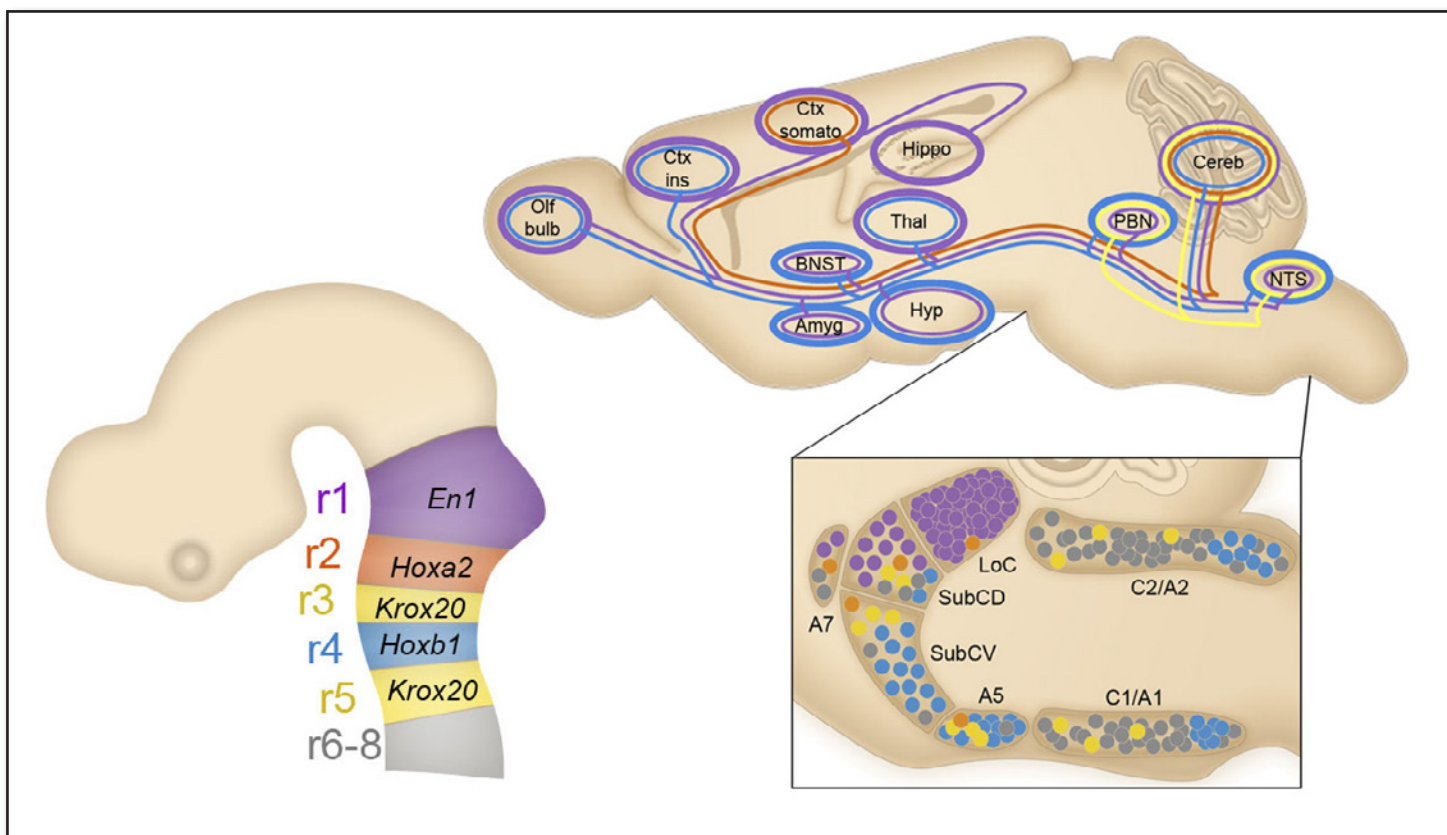


As a staff scientist in Jensen’s group, Plummer helps supervise the various research projects taking place in the lab. (Photo courtesy of Steve McCaw)



Jacqueline de Marchena, Ph.D., a postdoctoral fellow who works with Jensen, is also a co-author on the paper. de Marchena is a 2013 FARE award winner. (Photo courtesy of Steve McCaw)

Citation: Robertson SD, Plummer NW, de Marchena J, Jensen P. 2013. Developmental origins of central norepinephrine neuron diversity. *Nat Neurosci*; doi:10.1038/nn.3458 [Online 14 July 2013].



Using a technique called genetic fate mapping, Jensen's team labeled NE neurons in the fetal mouse brain, and tracked their progress during development. The graphic on the left shows the fetal brain with rhombomeres 1-8 distinguished by color, along with the expression of specific genes. The image on the right displays an adult mouse brain, which includes the location of rhombomere-derived NE neurons in the hindbrain (inset box). The colored lines in the upper portion depict the NE neuronal projections throughout the brain. (Design and artwork by Patricia Jensen, Sabrina Robertson, and Sue Edelstein)

[Return to Table of Contents](#)

Promising environmental health researchers receive Superfund award

By Sara Mishamandani

Five exceptional NIEHS-funded Superfund Research Program (SRP) trainees received the 2013 [K.C. Donnelly Externship Award Supplement](#), to enrich their research in environmental health science at another institution. Now in its third year, the annual award was established to honor environmental health researcher and Superfund grantee Kirby (K.C.) Donnelly, Ph.D.

Audrey Bone

Bone is a graduate student at the Duke University SRP, under the guidance of Richard Di Giulio, Ph.D. Her current research project involves evaluating the effects of nanomaterial-based degradation on toxicity of polycyclic aromatic hydrocarbons (PAHs). She will



"Acquiring the skill of properly executing the zebrafish assay, and analyzing the subsequent data, will not only advance my current project, but will provide a tool that I will be able to use in my career as an environmental toxicologist," said Bone. (Photo courtesy of Audrey Bone)

be conducting a six-week externship at Oregon State University (OSU), where she will learn to use the zebrafish developmental toxicity bioassay and molecular tools developed at OSU to understand the toxicity pathways associated with byproducts from PAH degradation by nanoparticles. Robert Tanguay, Ph.D., will provide mentorship while she is there.

Leah Chibwe

Chibwe is a graduate student at the OSU SRP, under the guidance of Staci Simonich, Ph.D. She will complete a three-month externship at the University of North Carolina at Chapel Hill (UNC) with Michael Aitken, Ph.D. Chibwe will work to identify potentially genotoxic compounds in bioremediated soil, originally contaminated with PAHs. She plans to conduct the novel DT40 bioassay to characterize genotoxicity associated with pre-remediated and post-remediated soil samples. She will also investigate whether parent PAHs are converted to oxygenated PAH byproducts, which are more water-soluble, bioavailable, and potentially more toxic.

Shohreh Farzan, Ph.D.

Farzan is a postdoctoral researcher at the Dartmouth Toxic Metals SRP, under the guidance of Margaret Karagas, Ph.D. She will complete a three-month externship at New York University with Yu Chen, Ph.D., in collaboration with the Columbia University SRP. Using existing data from the Health Effects of Arsenic Longitudinal Study cohort in Bangladesh and data from Karagas' New Hampshire arsenic studies, Farzan will examine the role of arsenic exposure on blood pressure over time and in relation to cardiovascular disease-related mortality.

Erin Madeen

Madeen is a graduate student in the OSU SRP, under the mentorship of David Williams, Ph.D. She will complete a three-week externship at the Lawrence Livermore National Laboratory in California with Ted Ognibene, Ph.D. Madeen will be conducting analysis of high molecular weight PAHs in blood and urine from human volunteers, following microdosing with environmentally relevant amounts of labeled PAHs. She will learn to use moving wire technology, a high-performance liquid chromatography system that can separate individual metabolites coupled to accelerator mass spectrometry, for metabolite quantitation.

Honoring a mentor and a scholar with generous externship support

Donnelly, who died in 2009 after a distinguished career with the Department of Environmental and Occupational Health at the Texas A&M Health Science Center School of Rural Public Health, was a dedicated mentor to his students and postdoctoral researchers, instilling in them the importance of applying their knowledge and findings to improve the health of communities exposed to environmental contaminants. To honor Donnelly, the award supports SRP graduate students and postdoctoral fellows who are pursuing transdisciplinary research, and emphasizes the importance of research application and collaboration to promote human health.

The award provides the SRP trainees with up to \$10,000 to fund supplies, travel, housing, and costs for research, training, and collaboration at other SRP centers, government laboratories, and state, local, or tribal agencies, for up to three months.



"This externship will give me the opportunity to learn about the operation of the UNC lab-scale bioreactor and the DT40 bioassay technique at UNC to evaluate the human health impacts of PAHs at Superfund sites," said Chibwe. (Photo courtesy of Leah Chibwe)

James Rice, Ph.D.

James Rice is a postdoctoral research associate with the Brown University SRP, under the guidance of Eric Suuberg, Ph.D. Rice will conduct a three-month research externship at the Fisherville Mill Brownfield site in Grafton, Mass., with Robert Burgess, Ph.D., a staff scientist at the U.S. Environmental Protection Agency. Rice will lead a passive sampler study in the Blackstone River at the Fisherville Mill site, to monitor contamination of heating oil, containing petroleum hydrocarbons, and other potential pollutants.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)



"I am eager to train with Dr. Yu Chen, who will help me to develop a more diverse skill set, as well as expose me to an area of research that has broad applications for future work," said Farzan.
(Photo courtesy of Shohreh Farzan)

[Return to Table of Contents](#)



"Moving wire is a new technology, and our project is the first metabolite study on this system," said Madeen. Lawrence Livermore National Laboratory is in a unique position to provide valuable training that I can bring back to my laboratory at OSU. We will rely heavily on the moving wire platform for future projects."
(Photo courtesy of Erin Madeen)




"This externship will enhance my research skills and knowledge of an exciting and innovative environmental sampling technique," said Rice. "It will also be my first opportunity to partner with and conduct research at a government laboratory, providing me with experience connecting academic research to government and professional practice."
(Photo courtesy of James Rice)

PEPH webinar focuses on the health of our oceans



By Audrey Pinto

The NIEHS Partnerships for Environmental Public Health (PEPH) program hosted a webinar July 10 highlighting some of the cutting-edge marine research being conducted at two Centers for Oceans and Human Health (COHH), funded by NIEHS and the National Science Foundation (NSF). NIEHS Program Administrator [Fred Tyson, Ph.D.](#), led the webinar.

Scientists leading the research teams at these centers — [John Stegeman, Ph.D.](#), of the Woods Hole Oceanographic Institution and [Bradley Moore, Ph.D.](#), of the Scripps Institution of Oceanography — presented their objectives, reported preliminary data, and proposed ways to meet future challenges.



Linked video:
[Watch a video about the Scripps Center for Oceans and Human Health \(04:05\)](#)
(Launches in new window)

Download Media Player:  Flash 

Both presentations captured the immediacy of issues involving oceans and human health, and pointed to effects of global climate change that will almost certainly increase the impact of the aquatic environment on humans. The more scientists learn about the oceans, Stegeman and Moore agreed, the more they realize how much still remains to be learned about its mysteries, including naturally occurring neurotoxins and hazardous compounds that may be created in the oceans themselves.

In the spirit of the NIEHS mission to take a multidisciplinary approach in public health research, the centers are engaging diverse teams of basic, translational, and applied scientists, ranging from chemists, biologists, and environmental health scientists, to physicians, pharmacists, and public health professionals. Using this meta-disciplinary approach, both teams are attempting to answer some perplexing questions regarding harmful algal blooms (HABs) and halogenated organic compounds (HOCs), to understand the interconnections between human health and marine environments.

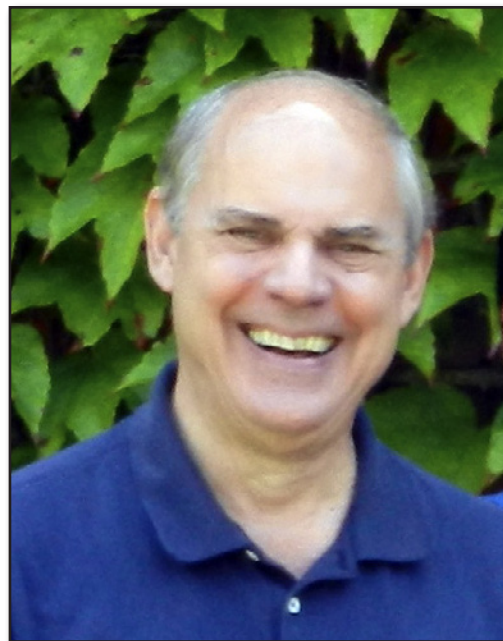
Understanding the dynamics of toxic *Alexandrium*

Stegeman began his presentation by observing, “Human health and well-being are fundamentally and inextricably linked to the oceans.” To identify potential threats to marine and human health, his NSF and NIEHS-funded team is studying [population dynamics of HABs](#), by modeling the biological and physical processes of two key species — *Alexandrium fundyense*, which produces [saxitoxins](#) and *Pseudo-nitzschia spp.*, which produce [domoic acid](#). These species are responsible for different types of shellfish poisoning, and may have the potential to significantly impact human health worldwide.

As Stegeman explained, “Factors affecting the distribution, survival, proliferation, and toxicity of HAB species are still poorly understood.” To better understand these factors, his research team is applying state-of-the-art remote sensor technology — imaging flow cytometry and an Environmental Sample Processor that detects DNA sequences — in two different locations in New England — a marsh environment and the Gulf of Maine. The center studies are yielding new information about HAB processes and the mechanisms of toxin action that are accompanied by, and compared with, important toxicants introduced by humans that are common in marine environments.

Evidence of naturally occurring PBDEs with a marine connection

With [NIEHS support](#), Moore’s research team at Scripps is advancing the knowledge of the biology and chemistry of marine contaminants of emerging concern. They are [tracking naturally occurring HOCs](#), which, until recently, were presumed to be manufactured



Both Stegeman, above, and Moore concluded that collaborative research and effective communication strategies are the fundamental components needed to address the complexities of marine environments and global climate change, and to determine the long-term consequence for humans and marine organisms. (Photo by Common Good Productions)



Along with his grant to research HOCs, Moore is also lead researcher for the Center for Marine Biotechnology and Biomedicine at Scripps, which has the meta-disciplinary advantage of being located adjacent to a university with a medical school and school of pharmacy. (Photo courtesy of Bradley Moore)

by humans in the form of persistent organic pollutants (POPs) used in electronics and flame retardants — specifically polybrominated diphenyl ethers (PBDEs) and polybrominated biphenyl ethers.

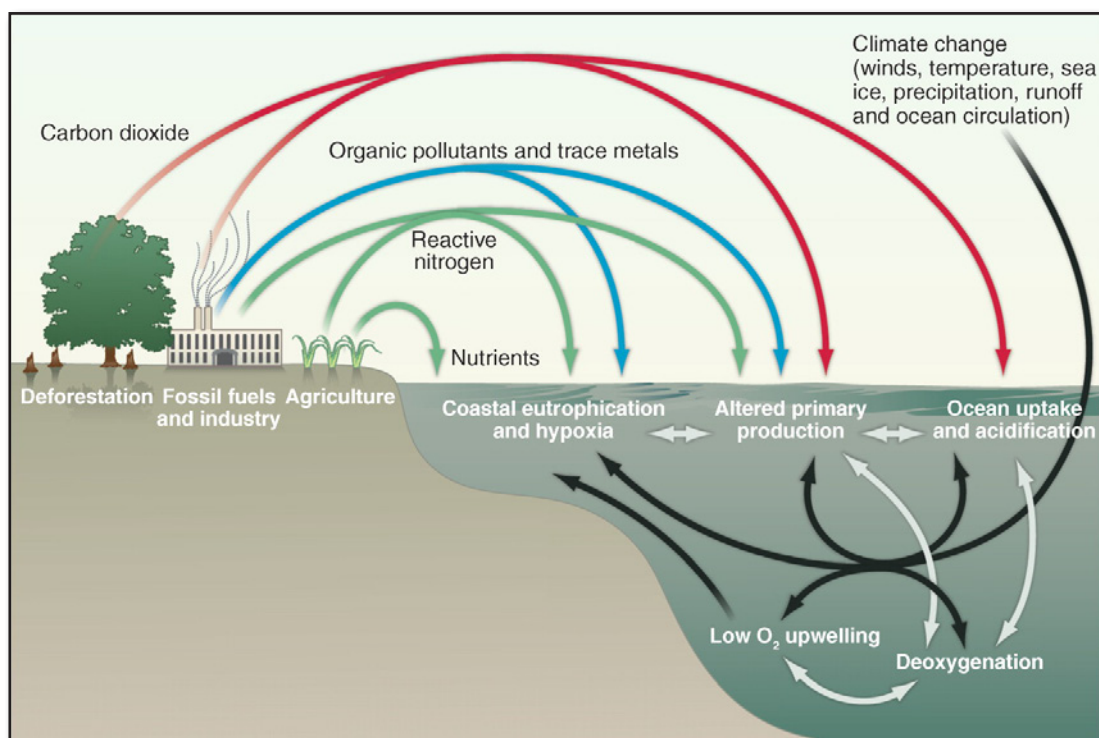
Now, evidence suggests that there may be natural versions of HOCs that are structurally related to man-made PBDEs, but form a new class of compounds. These new chemicals have been identified in marine mammals, such as seals and dolphins, and fish, such as tuna and swordfish — food sources consumed by humans.

Although the toxic effects of man-made PBDEs are well known and linked to different human diseases, the origin and transmission of natural POPs in marine environments are poorly understood. Moore went on to point out that no natural sources, or sinks, for POPs have yet been identified, but, because of global climate change, they may be increasing, and may become more important in terms of the suite of POPs people ingest through seafood in their diets.



Along with his lead in the COHH program, Tyson also serves as the NIEHS program administrator for the [NIH Roadmap Epigenomics Program](#) and the Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) Program. (Photo courtesy of Steve McCaw)

(Audrey Pinto, Ph.D., is technical editor for the journal *Environmental Health Perspectives*.)



Stegeman used this schematic to illustrate the human impacts on ocean biogeochemistry, either directly via fluxes of material into the ocean (colored arrows), or indirectly via climate change and altered ocean circulation (black arrows). The gray arrows denote the interconnections among ocean biogeochemical dynamics. Note that many ocean processes are affected by multiple stressors, and the synergistic effect of human perturbations is a key area for further research. (Originally published in [Doney SC. 2010. The growing human footprint on coastal and open-ocean biogeochemistry. Science 328\(5985\): 1512-1516. This image is used for educational purposes only. Courtesy of Scott Doney and Science](#))

This month in EHP

This month, [Environmental Health Perspectives \(EHP\)](#) highlights efforts to reduce pollution caused by artisanal brick kilns, and implications of a Supreme Court ruling for genetic research.

Modernizing Artisanal Brick Kilns to Curb Environmental Health Impacts

Most of the millions of bricks made each year in developing countries are fired in highly polluting artisanal kilns. Since brick production keeps pace with population growth, its environmental health impacts are likely growing throughout the developing world. A number of small-scale and multinational development groups, coordinated by the World Bank, the United Nations, and other organizations, are now turning their attention to modernization efforts in this important, but poorly characterized, industrial sector.

Our Shared Code: The Myriad Decision and the Future of Genetic Research

In its June 2013 decision in *Association for Molecular Pathologists, et al. v. Myriad Genetics, Inc., et al.*, the U.S. Supreme Court ended the decades-old practice of granting patents on isolated DNA, although cDNA, synthesized in the laboratory, is still eligible for patent. The decision has been widely lauded as a victory for patients, scientists, and clinicians, but the patent eligibility of cDNA and Myriad's sequestration of its data in a proprietary database have unclear implications for genomic studies.



<http://twitter.com/ehponline>



Featured research and related news articles this month include:

- **Fetal Exposure of Rhesus Macaques to Bisphenol A Alters Conducting Airway Cellular Development by Changing Epithelial Secretory Product Expression** — BPA and Altered Airway Cells: Association Seen in Rhesus Macaques after Third-Trimester Exposure
- **Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment** — Germ Warfare? Strategies for Reducing the Spread of Antibiotic Resistance
- **Understanding and Managing Zoonotic Risk in the New Livestock Industries** — Infectious Diseases Associated with Livestock Production: Mitigating Future Risks
- **High Bioavailability of Bisphenol A from Sublingual Exposure** — Oral Argument: Sublingual Findings Challenge Key Assumptions about BPA Exposure

[Return to Table of Contents](#)

Extramural papers of the month

By *Nancy Lamontagne*

- [Mouse study points to possible gene-environment interaction for schizophrenia](#)
- [Improving health for low-income workers](#)
- [Metabolomics reveals early changes in metabolic pathways for Alzheimer's disease](#)
- [Brd4 insulates chromatin from DNA damage signaling](#)

Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Mouse study points to possible gene-environment interaction for schizophrenia

An NIEHS grantee reports that mice engineered with a genetic risk factor for schizophrenia, and exposed to lead during early life, showed schizophrenia-like behaviors and structural changes in their brains. The findings suggest a gene-environment interaction is at work, and supports the hypothesis that environmental contaminants could contribute to the development of mental disorders in susceptible people.

Recent studies in people suggest a possible association between prenatal exposure to lead and increased likelihood of developing schizophrenia later. To find out more, the researchers looked at the consequences of lead exposure on mice with a mutant form of the human disrupted-in-schizophrenia-1 (mDISC1) gene, which is a risk factor for major psychiatric disorders. The mDISC1 mice that received lifelong exposure to lead showed schizophrenia-like behaviors and brain changes. These mice also had stronger responses to an N-methyl-D-aspartate receptor (NMDAR) antagonist. Some scientists hypothesize that NMDAR is an important factor in the pathophysiology of schizophrenia, and lead is a strong and selective antagonist of the NMDAR.

Citation: [Abazyan B, Dziedzic J, Hua K, Abazyan S, Yang C, Mori S, Pletnikov MV, Guilarte TR. 2013. Chronic exposure of mutant DISC1 mice to lead produces sex-dependent abnormalities consistent with schizophrenia and related mental disorders: a gene-environment interaction study. Schizophr Bull; doi:10.1093/schbul/sbt071. \[Online 28 May 2013\]. \[Story\]\(#\)](#)

[Return to Table of Contents](#)

Improving health for low-income workers

An NIEHS grantee co-authored a paper that calls for improving the health of low-income workers, by integrating health protection and health promotion programs that can be delivered at worksites, state and local health departments, community health centers, and community-based organizations. Low-income workers experience overlapping occupational and nonoccupational risks that can be worsened by limited resources and societal racism.

The authors present a social ecological framework for creating programs that bring together health protection and promotion. This framework examines how various levels of influence — intrapersonal, interpersonal,

institutional, community/society, and policy — can impact health. They provide six broad recommendations for reducing health inequities among low-income workers — improve access and quality of work-related data; integrate work environmental factors into care at community health centers; improve the exchange of information and ideas; increase the integration of health and occupational health education and training; test and evaluate new approaches; and improve worker and community engagement.

The authors emphasize the importance of integrated public health programs that control unhealthy exposures, promote healthy lifestyles, and encourage healthy decisions. They also stress that employers, workers, and advocates need to work with public health practitioners to deliver health protection and promotion programs at the workplace or in the community.

Citation: Baron SL, Beard S, Davis LK, Delp L, Forst L, Kidd-Taylor A, Liebman AK, Linnan L, Punnett L, Welch LS. 2013. Promoting integrated approaches to reducing health inequities among low-income workers: applying a social ecological framework. *Am J Ind Med*; doi:10.1002/ajim.22174 [Online 26 March 2013].

[Return to Table of Contents](#)

Metabolomics reveals early changes in metabolic pathways for Alzheimer's disease

With funding from NIEHS, researchers found changes in the metabolic pathways of Alzheimer's patients that were detectable in blood plasma. The findings suggest that it might be possible to identify plasma biomarkers for early Alzheimer's disease diagnosis, monitoring disease progression, and evaluating therapeutic approaches.

The researchers used a nontargeted metabolomics approach, based on liquid chromatography and mass spectrometry, to analyze cerebrospinal fluid (CSF) and plasma samples from 45 people enrolled in studies at the Mayo Clinic — 38 in the Study of Aging and 7 in the Alzheimer Disease Research Center. Study participants included 15 people with no cognitive decline, 15 with mild cognitive impairment, and 15 with Alzheimer's disease.

In total, the investigators found 342 metabolites in the plasma and 351 in the cerebrospinal fluid that were significantly altered. When looking at differences between the Alzheimer's disease group and cognitively normal group, they found altered cholesterol and sphingolipids transport in both cerebrospinal fluid and plasma. Patients with mild cognitive impairment and Alzheimer's disease showed significant impairment in energy metabolism, Krebs cycle, mitochondrial function, neurotransmitter and amino acid metabolism, and lipid biosynthesis pathways. As disease severity increased, so did the number of affected pathways for both fluids. Importantly, the changes observed in plasma accurately reflected the changes in cerebrospinal fluid (CSF), showing that the biomarkers in the plasma reflected the brain differences of the study participants. The researchers say that additional research using targeted metabolomics could identify specific panels of biomarkers.

Citation: Trushina E, Dutta T, Persson XM, Mielke MM, Petersen RC. 2013. Identification of altered metabolic pathways in plasma and CSF in mild cognitive impairment and Alzheimer's disease using metabolomics. *PLoS One* 8(5):e63644.

[Return to Table of Contents](#)

Brd4 insulates chromatin from DNA damage signaling

Researchers supported in part by the NIEHS, report evidence that an isoform of the bromodomain protein Brd4 can modulate the signaling response to DNA damage by insulating chromatin.

When DNA damage occurs, a network of signals directs various responses, such as stopping the progression of the cell cycle, recruiting factors needed for DNA repair or prompting programmed cell death. Problems with the cell's response to DNA damage can lead to tumor growth. The researchers studied the signaling and response of cells exposed to ionizing radiation damage, finding that Brd4 isoform B inhibited DNA damage response signaling. In cells with nonfunctioning Brd4 isoform B, the researchers observed a more relaxed chromatin structure and improved survival after irradiation.

Cells with functional Brd4 isoform B had more compact chromatin, lessened DNA damage response signaling, and enhanced radiation-induced lethality. From these findings, the researchers conclude that Brd4 facilitates structural changes in chromatin that lessen the DNA signaling response to ionizing radiation.

Citation: Floyd SR, Pacold ME, Huang Q, Clarke SM, Lam FC, Cannell IG, Bryson BD, Rameseder J, Lee MJ, Blake EJ, Fydrych A, Ho R, Greenberger BA, Chen GC, Maffa A, Del Rosario AM, Root DE, Carpenter AE, Hahn WC, Sabatini DM, Chen CC, White FM, Bradner JE, Yaffe MB. 2013. The bromodomain protein Brd4 insulates chromatin from DNA damage signalling. *Nature*. 498(7453):246-250.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

[Return to Table of Contents](#)

Intramural papers of the month

By Aleksandra Adomas, Heather Franco, Mallikarjuna Metukuri, and Bailey Schug

- [Ultraviolet radiation exposure associated with autoimmune diseases in juveniles](#)
- [Acrolein-induced adducts may cause mutations in mitochondria](#)
- [Interaction of Prox1 with RORs modulates circadian clock and metabolic regulatory networks in liver](#)
- [Mutations cause antagonist reversal activity of estrogen receptor alpha](#)

Ultraviolet radiation exposure associated with autoimmune diseases in juveniles

According to a new study conducted by the NIEHS Environmental Autoimmunity Group, ultraviolet radiation (UVR) from sunlight may be connected with the development of certain autoimmune diseases. The study examined whether there was a relationship between the level of ultraviolet exposure at illness onset, with the form of juvenile idiopathic inflammatory myopathies (IIMs), which are systematic autoimmune diseases characterized by muscle and skin inflammation.

To conduct the study, the researchers assessed the relationship between UVR exposure in the month before symptom onset and the prevalence of juvenile dermatomyositis (JDM), compared to juvenile polymyositis (JPM), in 298 juvenile IIM patients, and in JDM patients, the association between UVR and presence of myositis autoantibodies. They found an association between UVR and JDM, as well as an association between UVR and the anti-p155 myositis autoantibody, a subgroup with photosensitive skin rashes. Also, regions of the United States with higher UVR had an increased prevalence of JDM and the anti-p155 autoantibody. These data suggest photoprotective prevention measures should be implemented. They caution that more research on the role of UVR in the pathogenesis of juvenile myositis is needed.

While the causes of autoimmune diseases are not known, emerging research suggests they develop after one or more environmental exposures in genetically susceptible people. This study adds UVR to the growing list of environmental exposures that may be contributing factors in the development of autoimmune diseases. **(BS)**

Citation: [Shah M, Targoff IN, Rice MM, Miller FW, Rider LG, Childhood Myositis Heterogeneity Collaborative Study Group](#). 2013. Brief report: ultraviolet radiation exposure is associated with clinical and autoantibody phenotypes in juvenile myositis. *Arthritis Rheum* 65(7):1934-1941.

[Return to Table of Contents](#)

Acrolein-induced adducts may cause mutations in mitochondria

NIEHS scientists, together with collaborators from the Oregon Health and Science University, demonstrated that, although the human DNA polymerase gamma can bypass lesions induced in mitochondrial DNA by acrolein, the subsequent replication process is inefficient and error prone. Since acrolein is a mutagenic aldehyde that is found in cigarette smoke, the research has implications for environmental exposures and human health.

Acrolein reacts with DNA bases to form lesions that, in the nucleus, are removed by repair mechanisms that do not exist in mitochondria. In fact, mammalian mitochondria contain a single polymerase, polymerase gamma, which handles both replication and repair processes.

The researchers used single nucleotide incorporation and primer extension assays to demonstrate that polymerase gamma was able to integrate correct nucleotide and process DNA extension, when acrolein-induced adduct was located in the major DNA groove. However, the enzyme was inefficient and error prone when the lesion was located in the minor groove. Polymerase gamma preferred to incorporate incorrect purine nucleotides and extension efficiency was negatively affected. The authors propose that acrolein produced internally by lipid peroxidation, or present in the environmental pollutants, can contribute to accumulation of somatic mutations in mitochondrial DNA and to age-dependent neurodegenerative disorders. **(AA)**

Citation: [Kasiviswanathan R, Minko IG, Lloyd RS, Copeland WC](#). 2013. Translesion synthesis past acrolein-derived DNA adducts by human mitochondrial DNA polymerase gamma. *J Biol Chem* 288(20):14247-14255.

[Return to Table of Contents](#)

Interaction of Prox1 with RORs modulates circadian clock and metabolic regulatory networks in liver

Scientists from the NIEHS Cell Biology Group identified the coregulator Prospero-related homeobox 1 (Prox1) as a novel interacting partner and modulator of the retinoic acid-related orphan receptors (RORs), which play a critical role in the regulation of genes involved in liver metabolism and circadian rhythm. As RORs have been implicated in the regulation of embryonic development, obesity, inflammation, and diabetes, understanding the mechanism of action of these proteins is relevant to several major human health issues.

Using multiple biochemical approaches, the researchers demonstrated that the interaction between Prox1 and RORs promotes the nuclear localization of the complex to target gene promoters, where it affects chromatin structure and inhibits target gene transcription. The interaction occurs through specific domains of the proteins and is stabilized by ROR antagonists. While Prox1 regulates the expression and activity of ROR gamma, inversely ROR gamma regulates the circadian oscillation of Prox1 expression, indicating that each protein regulates the other. Thus, Prox1 appears to be part of a feedback loop that negatively modulates ROR transcriptional activity and, as such, the regulation of clock and metabolic networks by RORs.

Because disruption of the circadian clock and perturbation of metabolic pathways have been implicated in the etiology of several diseases, including metabolic syndrome, these studies not only provide new insights into the regulation of metabolic syndrome, but may also lead to new intervention strategies. (HF)

Citation: [Takeda Y, Jetten AM](#). 2013. Prospero-related homeobox1 (Prox1) functions as a novel modulator of retinoic acid-related orphan receptors alpha- and gamma-mediated transactivation. *Nucleic Acids Res*; doi:10.1093/nar/gkt447 [Online 30 May 2013].

[Return to Table of Contents](#)

Mutations cause antagonist reversal activity of estrogen receptor alpha

In a recent study, NIEHS investigators have proposed a novel molecular mechanism by which estrogen receptor (ER) alpha antagonists modulate the ER alpha ligand binding domain (LBD) DNA binding activity and antagonist reversal activity.

ER alpha, a nuclear receptor ligand dependent nuclear transcription factor, has two transactivating functional domains (AF) — AF-1 and AF-2. AF-2 is distributed in the C-terminal LBD of the ER alpha protein. Helix 12 (H12) in the LBD is a component of the AF-2 and its configuration is ligand inducible to generate either an active or inactive form. H12 is needed for estradiol induced dimerization. Researchers have known that mutations that the ER alpha mutant, AF2ER, possessing L543A and L544A in H12 of ER alpha reverse antagonists, such as 4-hydroxytamoxifen, to agonists, but not the more effective antagonist fulvestrant/ICI182780 (ICI). In the present study, the authors analyzed the correlation between the ICI-dependent ER-mediated transcription activity of AF2ER, and AF2ER-LBD dimerization activity.

The results demonstrated that ICI-dependent AF2ER activation correlated with the activity of AF2ER-LBD homodimerization involving a unique and previously unrecognized region of the receptor protein involving the F-domain and not H12. Prevention of dimerization impaired the ICI-dependent estrogen-responsive

element binding and transcription activity of AF2ER, supporting a mechanism that antagonist dependent LBD homodimerization results in antagonist reversal activity of ER alpha. The authors propose that this mechanism may be associated with the partial agonist activity of selective ER modulators, which depends on the F-domain for the dimerization. (MM)

Citation: [Arao Y](#), [Hamilton KJ](#), [Coons LA](#), [Korach KS](#). 2013. Estrogen receptor alpha L543A, L544A mutation changes antagonists to agonists, correlating with the ligand binding domain dimerization associated with DNA binding activity. J Biol Chem 288(29):21105-21116.

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis. Heather Franco, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Reproductive and Developmental Toxicology. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction. Bailey Schug studies health promotion and nutrition at Appalachian State University and is an intern in the NIEHS Office of Communications and Public Liaison.)

[Return to Table of Contents](#)

Inside the Institute

NIEHS volunteers support science day camp

By Richard Sloane

The Durham (N.C.) Alumnae Chapter of Delta Sigma Theta Sorority held its eighth annual Science and Everyday Experiences (SEE) summer camp June 22, attracting more than 40 students, grades 4-9, from Durham area schools.

Regional volunteers, including staff from NIEHS, provided a stimulating experience for children and their parents, built around the theme “Preparing for STEM Careers in a Global Society.” Important funding came from the Durham Alumnae Chapter and PNC Bank.

A host of Delta’s dedicated volunteers led hands-on science activities for the students, carrying on the sorority’s century-long tradition of service to the community and its young people. In large part because of its community outreach efforts, the Durham Alumnae Chapter was honored as the 2013 South Atlantic Region Chapter of the Year.

Getting off to a fun and healthy start

The day began with a health and fitness warm-up led by NIEHS volunteer Shawn Jeter. The lively workout was similar to a Zumba class, with rhythmic music playing, as the children danced and exercised in unison outside the building. Smiles prevailed while laughter filled the air.

After a welcome from event chair Sharon Beard of NIEHS, the 43 children rotated through three scientific experiment modules. These hands-on exercises offered the students a broad and stimulating experience, by tapping into contemporary topics. As NIEHS volunteer Joan Packenham, Ph.D., said, “The experiments were designed to expose students to successful scientists and also excite the students about science.”

One group enthusiastically extracted DNA from strawberries, during an exercise led by biomedical engineer Matthew McCullough, Ph.D., of North Carolina A&T State University.



Johnson-Thompson, standing, offered parents tips for enriching the home environment. (Photo courtesy of Willis Page and Arvis Epps)

A broad range of community support

Other speakers included Kendra Tucker from the Burroughs Wellcome Fund, Gloria Woods-Weeks from the J.D. Clement Early College High School at North Carolina Central University, and Joan Barber, Ph.D., and Carol Stern from the North Carolina School of Science and Mathematics. All shared details regarding their respective programs, each designed to give promising young science, engineering, and math students a jump in preparing for their futures.

Unfortunately, Jacqueline Ellis, Ph.D., who was prominently featured on the agenda, was unable to attend. Ellis received her Ph.D. in molecular genetics from UNC in May 2013. She was a student who had participated in programs described at the workshop. Ellis clearly serves as a model for what can be accomplished when students have access to these kinds of enrichment activities.

A second group performed a computer exercise, “Get With Programming,” where each child wrote simple computer code on a laptop computer. Computer engineer Corey Graves, Ph.D., and industrial engineer Lauren Davis, Ph.D., of N.C. A&T led the session.

The third group, led by Nyote Calixte of the Durham Alumnae Chapter, was called “I Feel Good” and dealt in part with the importance of iron in our diet. Children separated iron from various foods, including fortified cereals, and studied mock samples of saliva, with assistance from NIEHS postdoctoral fellows Danielle Watt, Ph.D., and Georgette Charles, Ph.D.

Involving parents

Twelve parents attended their own session, moderated by Packenham and former NIEHS director of Education and Biomedical Research Development Marian Johnson-Thompson, Ph.D. Now an adjunct professor at the University of North Carolina at Chapel Hill (UNC), Johnson-Thompson also served as a featured presenter. She explained the importance of science and math for children, no matter what path they may take in life, and urged parents to foster their children’s well-being. “Do all you can in support and maintenance of your children’s physical and mental health, through healthy diet and lifestyle practices.”

“Make time for your children,” Johnson-Thompson also said. “Encourage them to participate in social activities, community service projects, and demonstrate to them the importance of giving their best in all academic pursuits, and sports activities, too.” She concluded with reference to her NIEHS years, speaking of protecting children from the broad range of environmental challenges we all face, including noise, chemical pollutants and toxins, allergens, and biological hazards.

The SEE program has positively touched more than 350 students and 100 parents, through its camps, and will continue making positive efforts to encourage and stimulate children in science, engineering, and math.

Contact Sharon Beard for information regarding future programs at sbeard28@nc.rr.com.

(Richard Sloane is an employee services specialist with the NIEHS Office of Management.)



Students began their morning with a health and fitness warm-up. (Photo courtesy of Willis Page and Arvis Epps)



Campers obviously enjoyed the hands-on exercise of extracting DNA from strawberries. (Photo courtesy of Willis Page and Arvis Epps)



Calixte, center, worked with students, as they tested for iron in the “I Feel Good” exercise. (Photo courtesy of Willis Page and Arvis Epps)



Charles, left, and Watt, standing center, were also leaders in the “I Feel Good” exercise. (Photo courtesy of Willis Page and Arvis Epps)



Graves gave students preliminary instructions for the “Get With Programming” exercise. (Photo courtesy of Willis Page and Arvis Epps)



Volunteers, shown in the back row, and campers came together at the end of another successful SEE experience. Several of the participants are in their second year at the camp. (Photo courtesy of Willis Page and Arvis Epps)

[Return to Table of Contents](#)

It's summertime and the visitors flock to NIEHS

By Eddy Ball

NIEHS welcomes visitors all year, but, when June arrives, the number of guests increases dramatically, as summer program students participate in tours of the Institute. The serious science continues as well, but the fresh and eager faces of young people, who are interns or visitors, become much more common in the halls, meeting rooms, cafeteria, and labs at NIEHS.

From June 3 to July 16 alone, the NIEHS Office of Science Education and Diversity (OSD) called on Institute scientists for help organizing programs and tours for teachers and 11 groups of students, ranging from youngsters in the John Avery Boys and Girls Club of Durham, N.C., summer program, to graduate students in their early to mid-twenties, studying at the North Carolina State University (NCSU) College of Veterinary Medicine.

Students learn not all vets treat livestock and companion animals

For the veterinary students' visit June 26, OSD Special Assistant for Community Engagement and Outreach John Schelp took advantage of a group of volunteers from among NTP's staff of veterinary scientists, including Cellular and Molecular Pathology Branch group leader [Dave Malarkey, D.V.M., Ph.D.](#), who organized the half-day program for the fourth time, and worked with Schelp, who led the 40-minute tour.

The 30 students were accompanied by NCSU faculty advisors Jody Gookin, D.V.M., Ph.D., and Sam Jones, D.V.M., Ph.D. Their program is aimed at encouraging veterinary students to consider alternative careers in clinical or basic research.

The visitors seemed to be fascinated by the fact that more than 20 veterinarians work for NIEHS and NTP, pursuing such veterinary specialties as pathology, laboratory animal care, and animal welfare. "The students really enjoy the program Dr. Malarkey puts together," said Gookin. "Many are also surprised to learn that part of the NIH is right in our own backyard."

Feedback from tour participants

The campus tours, Schelp said, usually include a slideshow and overview; NIH Summer Internship Program (SIP) presentation from NIEHS SIP coordinator Debbie Wilson; two or three career talks from young scientists; a walking tour of the main building; chance encounters along the route; and a lab visit and demonstration. In addition to summer, according to Schelp, fall and spring semesters are popular times for the tours.

NIEHS can depend on OSD and its volunteer scientists and staff to make the experience rewarding for visitors and their program leaders, as evidenced by comments Schelp has received after the tours.

"John, at this point in their lives, exposure to a place like NIEHS was extremely beneficial. Beyond that, learning about the agency and hearing about health, environment, and research from such a terrific advocate like you was invaluable."

Gidi Shemer, Ph.D.
University of North Carolina at Chapel Hill

"This was very much a learning experience for us all about the environment in which we live. Thanks so much for your dedicated community service."

Earle Manhertz,
White Rock Baptist Church

"Hi John: I want to write a serious thank you note for the wonderful tour that we had and for the presentations."

Faye Calhoun, D.P.A.,
North Carolina Central University

"Wanted to let you know how much we all enjoyed our tour today and to express how much was learned. The students have been raving about what a wonderful field trip experience this was and I truly thank you for all that you did to make this possible."

Gloria Green,
Granville Central High School

The program began with presentations by NTP Associate Director John Bucher, Ph.D., and NIEHS and NTP Director Linda Birnbaum, Ph.D., who were participating in the program for the first time. NIEHS cancer biologist John Roberts Ph.D., spoke enthusiastically about the current understanding of metastasis, and the excitement and pure fun of conducting basic research in the lab.

Joining Malarkey were other volunteers from NTP and NIEHS, who described alternative career opportunities for veterinarians in various areas of biomedical research. They included Angela King-Herbert, D.V.M.; David Kurtz, D.V.M., Ph.D.; Arun Pandiri, Ph.D.; Gregory Travlos, D.V.M.; and Michael Boyle, D.V.M.



Malarkey, right, and Jones, center with beard, joined the students on the stairs overlooking Lake Discovery on the NIEHS campus. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)



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